PROSPECTIVE RANDOMISED COMPARATIVE STUDY OF EFFICACY OF COMBINATION OF TRANEXAMIC ACID AND ETHAMSYLATE BY ORAL AND INTRAVENOUS ROUTES IN RELATION TO CONTROL OF BLEEDING IN CARDIAC SURGERIES.

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfilment for the award of the degree of

DOCTOR OF MEDICINE

IN

ANAESTHESIOLOGY

BRANCH X

INSTITUTE OF ANAESTHESIOLOGY AND CRITICAL CARE

MADRAS MEDICAL COLLEGE

CHENNAI - 600003

MAY 2019

CERTIFICATE

This is to certify that the dissertation titled, **"PROSPECTIVE RANDOMISED COMPARATIVE STUDY OF EFFICACY OF COMBINATION OF TRANEXAMIC ACID AND ETHAMSYLATE BY ORAL AND INTRAVENOUS ROUTES IN RELATION TO CONTROL OF BLEEDING IN CARDIAC SURGERIES"** submitted by **Dr. HEMALATHA R V** in partial fulfilment for the award of the degree of Doctor of Medicine in Anaesthesiology by the Tamil Nadu Dr. M.G.R. Medical University, Chennai., is a bonafide record of the work done by her in the INSTITUTE OF ANAESTHESIOLOGY AND CRITICAL CARE, Madras Medical College and Rajiv Gandhi Government General Hospital, during the academic year 2016-2019.

Prof. Dr. ANURADHA SWAMINATHAN
M.D., D.A.,
The Director,
Institute of Anaesthesiology & Critical Care,
Madras Medical College,
Government General Hospital,
Chennai – 600 003.

Prof. Dr. JAYANTHI. R
M.D., FRCP (Glasg)
The Dean,
Madras Medical College,
Government General Hospital,
Chennai – 600 003.

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled, **"PROSPECTIVE RANDOMISED COMPARATIVE STUDY OFEFFICACY OF COMBINATION OF TRANEXAMIC ACID AND ETHAMSYLATE BY ORAL AND INTRAVENOUS ROUTES IN RELATION TO CONTROL OF BLEEDING IN CARDIAC SURGERIES"** submitted by **Dr. HEMALATHA R V**, in partial fulfilment for the award of the degree of Doctor of Medicine in Anaesthesiology by the Tamil Nadu Dr. M.G.R. Medical University, Chennai., is a bonafide record of the work done by her in the **INSTITUTE OF ANAESTHESIOLOGY AND CRITICAL CARE,** Madras Medical College and Rajiv Gandhi Government General Hospital, during the academic year 2016-2019.

Prof.Dr.VELLINGIRI, MD, DA.
Professor of Anaesthesiology,
Institute of Anaesthesiology and critical care,
Rajiv Gandhi Govt. General Hospital**,**
Madras Medical College,
Chennai - 600 003.

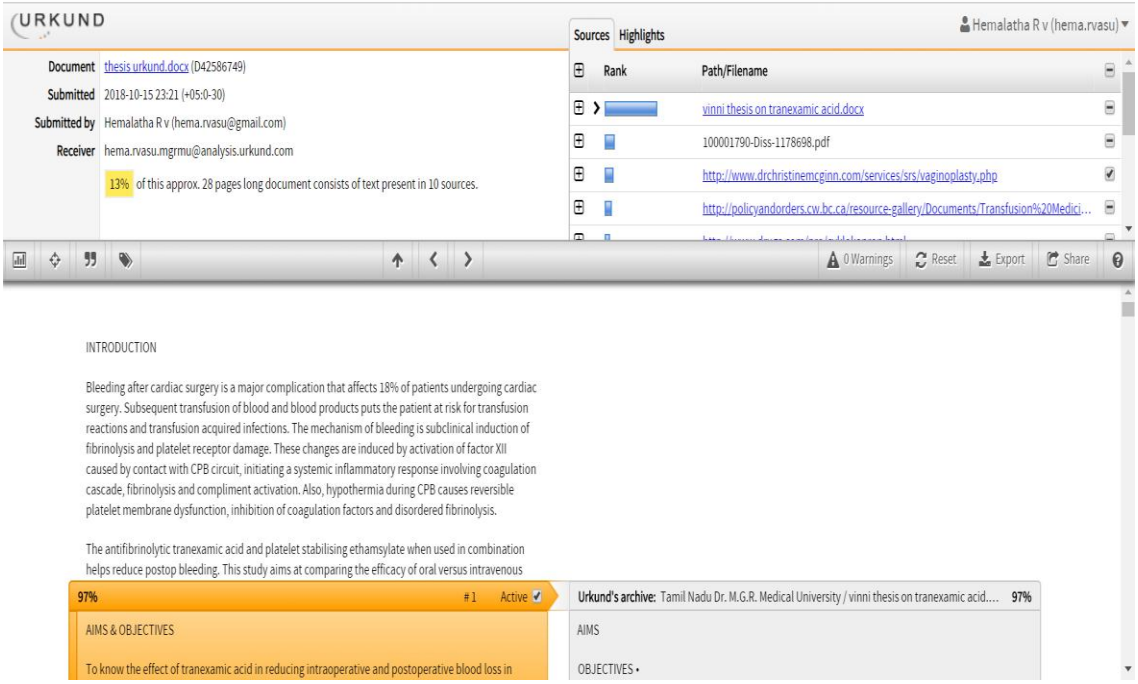
DECLARATION

I hereby, solemnly declare that this dissertation titled **"PROSPECTIVE RANDOMISED COMPARATIVE STUDY OF EFFICACY OF COMBINATION OF TRANEXAMIC ACID AND ETHAMSYLATE BY ORAL AND INTRAVENOUS ROUTES IN RELATION TO CONTROL OF BLEEDING IN CARDIAC SURGERIES"**, is a bonafide record of the work done by me in the **INSTITUTE OF ANAESTHESIOLOGY AND CRITICAL CARE,** Madras Medical College and Rajiv Gandhi Government General Hospital, during the academic year 2016-2019 under the guidance of **Prof.Dr.VELLINGIRI M.D., D.A.,** Professor of Anaesthesiology, Institute of Anaesthesiology and critical care, Rajiv Gandhi Govt. General Hospital**,** Madras Medical College, Chennai- 600 003 and submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Guindy, Chennai – 32**, in partial fulfilment of the requirements for the award of the degree of M.D. Anaesthesiology (Branch X), examinations to be held on April 2019. I have not submitted this dissertation previously to any university for the award of degree or diploma.

Place : Chennai **Dr. HEMALATHA R V**

Date :

URKUND.COM PHOTO



PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled **"PROSPECTIVE RANDOMISED COMPARATIVE STUDY OF EFFICACY OF COMBINATION OF TRANEXAMIC ACID AND ETHAMSYLATE BY ORAL AND INTRAVENOUS ROUTES IN RELATION TO CONTROL OF BLEEDING IN CARDIAC SURGERIES"** of the candidate **Dr.HEMALATHA R V** with registration number **201620008** for the award of **M.D.** in the branch of **ANAESTHESIOLOGY.** I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion 91 pages and the result shows **13 percentage** of plagiarism in the dissertation.

Prof. Dr.VELLINGIRI, M.D., D.A.,
Professor of Anaesthesiology,
Institute of Anaesthesiology and critical care,
Rajiv Gandhi Govt. General Hospital**,**
Madras Medical College,
Chennai - 600 003.

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I am thankful to the Institutional Ethics Committee for their guidance and approval of this study.

My sincere thanks to the statistician who played an important role in my study.

I am thankful to all my colleagues, family and friends for their moral support, help and advice in carrying out this dissertation.

Last but not the least; I thank all the parents of the patients for willingly submitting their children for this study.

Above all I pay my gratitude to the Lord Almighty for blessing me to complete this work.

CONTENTS

INTRODUCTION

INTRODUCTION

Bleeding after cardiac surgery is a major complication that affects 18% of patients undergoing cardiac surgery. Subsequent transfusion of blood and blood products puts the patient at risk for transfusion reactions and transfusion acquired infections. The mechanism of bleeding is subclinical induction of fibrinolysis and platelet receptor damage. These changes are induced by activation of factor XII caused by contact with CPB circuit, initiating a systemic inflammatory response involving coagulation cascade, fibrinolysis and compliment activation. Also, hypothermia during CPB causes reversible platelet membrane dysfunction, inhibition of coagulation factors and disordered fibrinolysis.

The antifibrinolytic tranexamic acid and platelet stabilising ethamsylate when used in combination helps reduce post operative bleeding. This study aims at comparing the efficacy of oral versus intravenous combination of the above said drugs in controlling blood loss.

AIM OF THE STUDY

AIMS & OBJECTIVES

To know the effect of tranexamic acid in reducing intraoperative and postoperative blood loss in patients undergoing cardiac valve replacement surgeries.

The secondary purpose of the study is

1. To know the requirement of transfusion intraoperatively and post operatively.
2. To study the effect of drug on haematocrit change after surgery.
3. To compare the cost effectiveness of the 2 groups.

PHARMACOLOGY

OF TRANEXAMIC ACID

PHARMACOLOGY OF TRANEXAMIC ACID

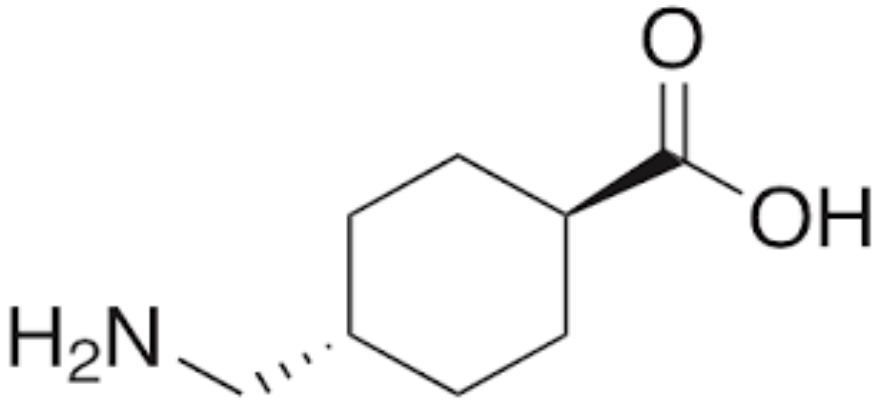
It is an antifibrinolytic agent with the chemical name Trans-4-(aminomethyl) cyclohexane carboxylic acid.

pH = 6.5 – 8.0

EMPERICAL FORMULA = $C_8H_{15}NO_2$

MOLECULAR WEIGHT = 157.2

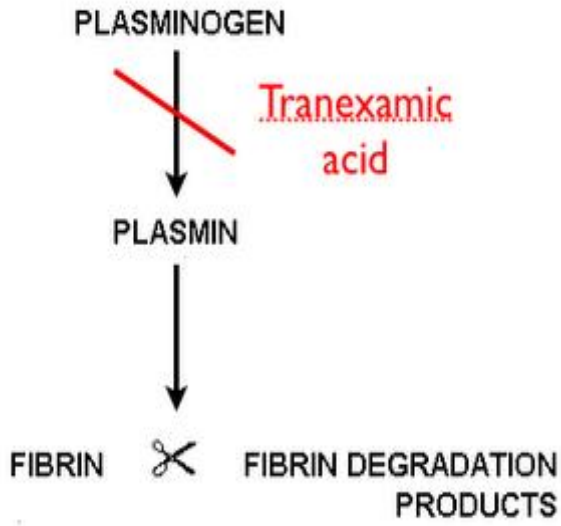
STRUCTURAL FORMULA



MECHANISM OF ACTION:

- It is a synthetic lysine derivative that inhibits fibrinolysis by blocking the lysine binding sites on plasminogen.
- It is a competitive inhibitor of plasminogen activation and at higher concentrations, a non- competitive inhibitor of plasmin. This action is similar to that of epsilon-aminocaproic acid but tranexamic acid is 10 times more potent.

- In concentrations of upto 10mg/ml it has no effect on platelet counts, clotting time or clotting factors in whole blood. But in concentrations of 10mg/ml to 1g/ml it prolongs thrombin time.



PHARMACOKINETIC AND PHARMACODYNAMICS:

Plasma protein binding is almost equal to 3% and mainly binds to plasminogen mainly and does not bind to albumin. The half life of intravenous dose of 1g is 2hours. The antifibrinolytic concentration remains in different tissues for 17hours and in serum for upto 7-8hours.

Volume of distribution is about 9 to 12 L. Elimination is mainly via glomerular filtration. Renal clearance is 110 – 116ml/min and more than 95% of the drug is excreted in urine unchanged. Following administration of drug intravenously at the dose of 10mg/kg body weight, excretion is almost 90% at 24hours.

Tranexamic acid can cross the placenta and it is secreted into the breast milk at a concentration of 1/100th of plasma concentration.

INDICATIONS:

I. MEDICAL:

- Hereditary angioneurotic edema[1]
- Upper gastro intestinal bleeding.[2,3]
- Reversal of drug induced bleeding (eg., TPA, Dabigatran, Rivaroxaban, Fondaparinux induced bleeding).
- Menorrhagia.[4,5]

II. ELECTIVE SURGERY

- Oral surgeries[6,7]
- Obstetrics and gynaecology surgeries for treatment of menorrhagia and post partumhaemorrhage[8,9,10]
- Cardiac surgeries: it decreases the blood loss without increasing the risk of thromboembolism.[11]
- Orthopaedic surgery: In joint arthroplasty and spine surgeries, there is evidence oral and intra-articular administration may be beneficial.[12,13]
- Liver: decreases transfusion in liver surgeries – resection and transplant surgeries.
- ENT/ Maxillo facial surgeries: decreases the total blood loss in tonsillectomy patients. It is used to treat epistaxis.

- Neuro surgeries: decreases the rate of re-bleeding[14,15]
- Urology: decreases the blood loss after TURP and serious hematuria.[16]
- It is also used to treat major hemoptysis.

III. TRAUMA:

Fibrinolysis is a recognized early feature of severe trauma which requires transfusions in trauma ward. Tranexamic acid is a reliable safe and most effective treatment.[17,18,19]

CONTRAINDICATIONS:

- Acquired defective colour vision.
- Subarachnoid haemorrhage.
- Patients with active intravascular clotting.
- Hypersensitivity to tranexamic acid.

PRECAUTIONS:

- Dose reduction is to be considered in patients with renal insufficiency.
- This drug may cause dizziness.
- In patients with history of thromboembolism there is increased risk of venous and arterial thrombosis
- Retinal artery and vein obstruction have also been reported.

DRUG INTERACTIONS:

There is no data regarding interactions with other drugs.

PHARMACOLOGY

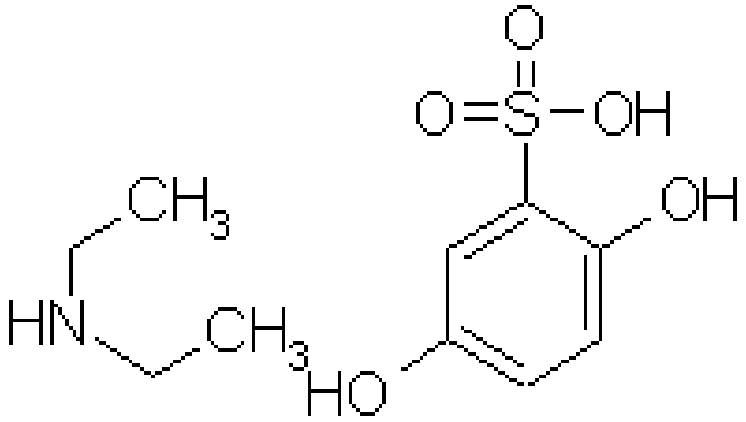
OF ETHAMSYLATE

PHARMACOLOGY OF ETHAMSYLATE

It is a hemostatic, non-thrombogenic agent discovered by Esteve et al in 1959.

CHEMICAL FORMULA: 2,5dihydroxy-benzene-sulphonate diethyl ammonium salt.

STRUCTURAL FORMULA:



MECHANISM OF ACTION:

- Ethamsylate is a synthetic hemostatic drug which acts on the first step of hemostasis by improving the platelet adhesiveness and restoring capillary resistance.
- Sack & Cerutti[20] showed that "ethamsylate decreases electrophoretic mobility of platelets and suggested that a reduction in negative membrane charge allowed formation of bridges between adjacent platelets in stirred systems."

- It promotes p-selectin dependent platelet adhesion.
- It is found to inhibit prostaglandin biosynthesis independent of cyclooxygenase inhibition.
- It has no vasoconstrictor action, it does not influence fibrinolysis or modify the plasma coagulation factors.

PHARMACOKINETICS:

ORAL ADMINISTRATION:

- Oral dose of 500mg leads to plasma concentration of 60 micrograms/L after 4hours with 95% bound to plasma proteins. Free plasma concentration of drug is 3micrograms/L.
- Plasma half life is 3.7hours.
- Elimination half life is 8hours and excreted unchanged in urine.
- It crosses placenta and is not known to be secreted in breast milk.

INTRAVENOUS ADMINISTRATION:

- 500mg of intravenous ethamsylate leads to maximum plasma levels of 50micrograms/ml reached within 10min of administration.
- Plasma half life is 1.9hours
- Elimination half life is 2hours and 85% is excreted in first 24hours.

INDICATIONS:

- Menorrhagia[21]
- Periventricular hemorrhage in low birth weight babies[22,23]
- Surgical and post surgical bleeding control[24,25]:
    - Tonsillectomy
    - Cataract surgeries
    - Prostatectomy[26]
    - Vaginal surgeries
    - Total hip replacements[27]
    - Aspirin induced gastric mucosal bleeding.

SIDE EFFECTS:

Most common side effects include nausea, gastritis, headache and skin rashes. Most of these disappear spontaneously. Earlier DVT was thought to occur in patients treated with ethamsylate but in a study conducted by Symes et al, it was concluded that "there is no clinical evidence of DVT in ethamsylate or placebo group."

CONTRAINDICATIONS:

- Acute porphyria
- Safer to avoid in first trimester of pregnancy.

DRUG INTERACTIONS:

There is no data regarding interactions with other drugs.

STORAGE:

- Protect the ampuoles from light.
- Discard if the solution is coloured.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

- De Reynier (1965) in his study administered 250mg ethamsylate intramuscularly and 250mg intravenously 1 hour before surgery, followed by 250mg intravenous just before induction and found a mean reduction of blood loss of 27 % of adults.
- Papatheodossiou (1973) investigated the effect of ethamsylate on peri and postoperative blood losses in 200 cases of tonsillectomy (ethamsylate was given before and after surgery) the results of which showed a mean blood loss of 4.86 ml in the ethamsylate group, against 27.5 ml in the placebo group. Two cases under placebo had postoperative hemorrhages (Papatheodossiou, 1973).
- Arora and Manford (1979) found that secondary hemorrhage was significantly less in children treated with ethamsylate. It is difficult to compare the results of these trials, as they all differ in some respects. For instance, operative blood losses were small in the placebo group of Arora and Manford (1979) compared with those reported by other authors carrying out dissection tonsillectomy and curettage of the adenoids under general anaesthesia in children. Another factor is the considerable inter-individual variation in blood loss within the groups, eg. different surgeons carrying out operations.
- In 1975, Symes et al.[26] performed a double-blinded trial in 76 patients (in the ethamsylate group, 1 g ethamsylate was intravenously given in the anaesthetic room, followed by 250 mg intramuscularly at 4 hourly intervals

until micro hematuria was ceased), where: median loss of blood at operation was 17 ml in those given ethamsylate compared with 72 ml in the placebo group ($p < 0.001$). median postoperative blood loss was 38 ml in the ethamsylate group, and 103 ml in the placebo group ($p < 0.05$).

- Four double-blind trials were designed to investigate the therapeutical efficacy of ethamsylate in dysfunctional uterine bleeding, with positive results in all four studies (Jaffe and Wickham, 1973; Harrison and Campbell, 1976; Kovacs and Annus, 1978; Levrier et al., 2003). Of these, Harrison and Campbell (1976) found that ethamsylate reduced mean menstrual blood loss more in patients with primary menorrhagia (-50%) than in women using intrauterine devices (-19%; ethamsylate was given in 2x250 mg tablets, four times a day, starting 5 days before the anticipated onset of menstruation and continuing for 10 days).
- Keith[27] has demonstrated that intravenous ethamsylate administered prior to the induction of anaesthesia does not reduce the average volume of blood lost during and after total hip replacement under lumbar epidural anaesthesia. He has suggested that the effect of ethamsylate may decrease as the degree of tissue trauma and haemorrhage increases.
- The Blood Conservation Using Antifibrinolytics in a Randomized Trial – BART Trial was published by Fergusson et al. compared the use of aprotinin, TXA and E-ACA in high-risk cardiac surgery patients and found that the 30-day mortality rate was 6% for the aprotinin group vs 3.9% for TXA (RR 1.55) and 4.0% for E-ACA (RR 1.52). BART protocol used

tranexamic acid regimen of 30 mg/kg loading dose followed by 16mg/kg/hr infusion during surgery with an added 2 mg/kg in the circuit (high dose range).

- Horrowet al.[28] undertook studies in cardiac surgeries and found that a prophylactic loading dose of 10mg/kg with infusion at 1mg/kg/hr was optimal, when compared to six incremental loading doses from 2.5 to 40 mg/kg followed by 0.25 mg to 4 mg/kg/ h infusion. A recent RCT pitted the Horrow regimen against the higher BART regimen in cardiac surgery patients, and it was found that although a high dose of Tranexamic acid does not reduce the incidence of blood product transfusion up to day7 (63% low dose vs 60% high dose), it is more effective than a low dose of TXA in decreasing transfusion (2.5 vs 4.1 U), blood loss (590 vs 820 mL), and repeat surgery (2.5% vs 6%).
- A large retrospective analysis by Poeran et al. studied the perioperative use of TXA in knee or hip arthroplasty (n = 872416). Patients who received TXA had lower rates of blood transfusion (7.7 vs 20.1%), fewer thromboembolic events (0.6 vs 0.8%), and reduced incidence of acute renal failure (1.6 vs 1.8%) as well as combined complications (1.9 vs 2.6%). With an increasing dose of TXA (none, < 1 g, ~ 2 g and > 3 g), there were decreasing odds (OR 0.31 to 0.38) of blood transfusion, and no significant increased risk of complications.
- CRASH -2 Trial[17,18] was a large randomised double blinded placebo-controlled multicentre clinical trial that included 20211 adult trauma

patients in 274 hospitals in 40 countries with or at risk of severe bleeding. They were randomised into 2 groups – one with tranexamic acid and the other with placebo. It reported that TXA use resulted in a statistically significant reduction in the relative risk (RR) of all-cause mortality of 9% (14.5% vs. 16.0%; RR, 0.91; confidence interval [CI], 0.85–0.97; p _ 0.0035). It also reported a reduction in RR of death as a result of bleeding of 15% (4.9% vs. 5.7%; RR, 0.85; CI, 0.76–0.96; p _ 0.0077). Similarly, they reported an RR reduction in death as a result of bleeding on the day of randomization of 20% (2.8% vs. 3.5%; RR, 0.80; CI, 0.68–0.93; p _ 0.0036). It was in this group of most severely injured patients that use of TXA was associated with the greatest reduction in risk of death. The benefit of TXA was greater in patients treated within 3 hours of injury and in patients with a presenting systolic blood pressure of around 75 mm Hg compared with those with normal systolic blood pressures.

- A nested RCT within CRASH-2 by Perel et al. reviewed the rate of Intracranial hemorrhage growth in 270 patients, and they found no moderate benefits (total hemorrhage growth and/or new ischemic lesions) nor harmful effects with certainty in traumatic brain injury.
- Caglaret al.[10] were the first to study the effect of TA in myomectomy in a RCT, 50 women in each group. TA reduced with statistical significance the postoperative and total blood loss as well as duration of surgery compared to the control group but the blood transfusion requirements were similar in both groups.

MATERIALS AND METHODS

MATERIALS AND METHODS

The study was conducted at **Institute Of Anesthesiology And Critical Care, Madras Medical College** between October 2017 to March 2018, after obtaining institutional ethical committee approval. The aim of this study is to know the effect of tranexamic acid in reducing intraoperative and postoperative blood loss in patients undergoing cardiac valve replacement surgeries.

STUDY DESIGN:

Prospective, randomized, case control study.

INCLUSION CRITERIA:

- Elective surgery
- Who have given valid informed consent.
- Aged 18 to 60years

EXCLUSION CRITERIA:

- Known allergy to either of the drugs
- History/ evidence of coagulopathy and bleeding disorder
- Renal dysfunction (Creatinine > 1.5)
- Thromboembolic event 1yr prior to surgery
- Hemoglobin <8gm/dl
- Not satisfying inclusion criteria
- Lack of written informed consent
- Emergency surgery.

MATERIALS:

- 18G venflon needle
- 5ml syringe
- Tranexamic acid and ethamsylate oral and IV preparations
- Normal saline
- Other drugs used in routine general anesthesia and cardiac surgeries.

MONITORS:

- Heart rate
- NIBP
- IBP
- Pulseoximetry
- Capnography
- CVP

STUDY OUTCOME MEASURES:

- **PRIMARY OUTCOME MEASURES:**
    - Volume of Blood loss intraoperatively and postoperatively up to first 24hours.

- **SECONDARY OUTCOME MEASURES:**
    - Bleeding time, clotting time, platelet count.
    - Post-operative hemoglobin and hematocrit values
    - Number of packed cells transfused intraoperatively and postoperatively.

METHODOLOGY

All the patients were assessed in our assessment clinic and informed consent was obtained after explaining the study. Patients who didn't meet the inclusion and exclusion criterias were not included in the study.

Patients were randomly allocated according to computer generated tables into two groups. Group O (oral = 30 patients) received Tab. Ethamsylate 250 mg + Tab. Tranexamic acid 500 mg which was started 24 hours prior to surgery given at 8 hourly interval; Last dose given 2 hours prior to surgery with sips of water. Group I (Intravenous = 30 patients) received I.V. Ethamsylate 250 mg + I.V. Tranexamic acid 500 mg given at 2 hourly intervals with the first dose given at the time of induction.

On arrival of patient in operation room, monitors were connected and two peripheral lines were secured. All patients received Inj.Glycopyrrolate 0.2mg iv + inj. Midazolam 1-2mg iv + inj. Fentanyl 40mcg iv. Central line (right internal jugular vein predominantly) and arterial line (left radial artery predominantly) were cannulated and secured. Patients were induced with intravenous inj. Fentanyl at 5-7mcg/kg + inj.Thiopentone 1-2mcg/kg (sleeping dose of Thiopentone) and paralysed with inj.Vecuronium 0.08-0.12mg/kg and were intubated with appropriate size tubes and secured.

Anesthesia were maintained with nitrous oxide: oxygen = 2:2 and isoflurane or sevoflurane. Intraoperative blood loss in the form of soaked pads and gauze were noted and transfusions given were noted. Serial ABG and ACT

monitoring were done. Post operatively all patients were shifted to Intensive care unit for elective post operative and ventilation.

Postoperatively patients were monitored for blood loss(drain), hemoglobin, Bleeding time, clotting time upto 24 hours.

STATISTICAL ANALYSIS

The raw data were initially entered to Microsoft Excel 2010 and these spreadsheets were used for analysis in SPSS. Statistical analysis was done using SPSS version 20.0.

- Descriptive statistics were calculated as frequency, percentage, mean and standard deviation. Descriptive data were represented using various tables and graphs
- For all the statistical tests of significance, p value of <0.05 was considered to reject the null hypothesis.
- After the normality tests showed normal distribution of continuous variables, independent samples student 't' test was done to test the difference in means of continuous variables at various time intervals between the IV group and oral group.
- Paired 't' test was done to test the difference in means of continuous variables before and after surgery between the IV group and oral group.

For categorical nominal variables, Chi-square test was done to test the difference in proportion of the variables between the IV group and oral group.

For non-normally distributed continuous variable, the difference between medians was done using Mann-Whitney test.

ANCOVA test was applied to test the difference in mean levels of hemodynamic parameters (continuous dependent variable) in the post-operative period between the IV group and oral group (categorical independent variable) with baseline levels as covariate.

Repeated measures ANOVA was applied to test the difference in mean activated clotting time at various time intervals between the IV group and oral group (categorical independent variable used as between subjects factor) as ACT levels (continuous dependent variable) was measured thrice.

SAMPLE SIZE CALCULATION

According to a study done by Rajkumar et al, average blood loss was found to be 700ml in tranexamic acid group.

STUDY: Tranexamic acid in controlling the postoperative bleeding in open heart surgical patients – a study report.

Authored By: Satyavolu Rajkumar et al.

Published In: Indian journal thoracic and cardiovascular surgery, 2005; 21: 207-211

Assuming the blood loss in Group A to be 700 ml and to study a difference of 75 ml reduction in blood loss in Group B with a S.D of 100 ml in both groups, and using an alpha of 0.05 and equal allocation of subjects in each groups, to achieve 80% power, the minimum required sample size is 28 in each treatment arm..Total sample size required: 56

Sample Size For Comparing Two Means

Input Data

Confidence Interval (2-sided)	95%
Power	80%
Ratio of sample size (Group 2/Group 1)	1

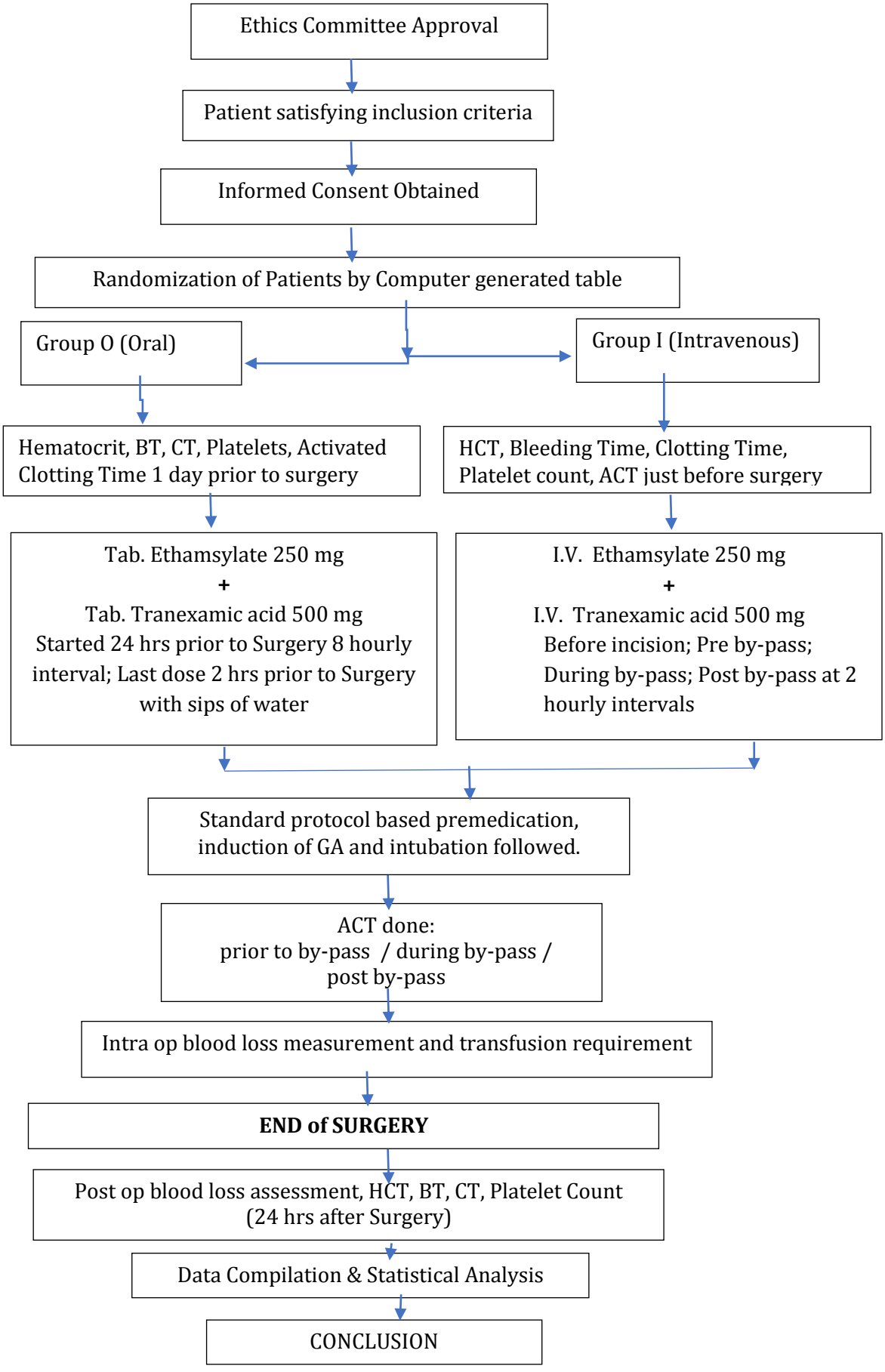
	Group 1	Group 2	Difference*
Mean	700	625	75
Standard deviation	100	100	
Variance	10000	10000	

Sample size of Group 1	28
Sample size of Group 2	28
Total sample size	56

*Difference between the means

Results from OpenEpi, Version 3, open source calculator--SSMean
Print from the browser with ctrl-P
or select text to copy and paste to other programs.

METHODOLOGY



OBSERVATION & RESULTS

Table 1: Age distribution of the study groups (n=60)

Age group	I.V Group n (%)	Oral Group n (%)	Total n (%)
20 - 30 years	4 (13.3)	6 (20)	10 (16.7)
31 - 40 years	11 (36.7)	9 (30)	20 (33.3)
41 - 50 years	5 (16.7)	6 (20)	11 (18.3)
51 - 60 years	10 (33.3)	9 (30)	19 (31.7)
Total	30 (100)	30 (100)	60 (100)

Mean (± S.D) Age of IV group: 42.57 ± 10.77

Mean (± S.D) Age of Oral group: 42.03 ± 11.458

Chi-square value: 0.744 p value: 0.863

Comments:

Age distribution of subjects in both the groups were comparable and the minimal difference observed was not statistically significant.

Fig 1: Age distribution of the study groups (n=60)

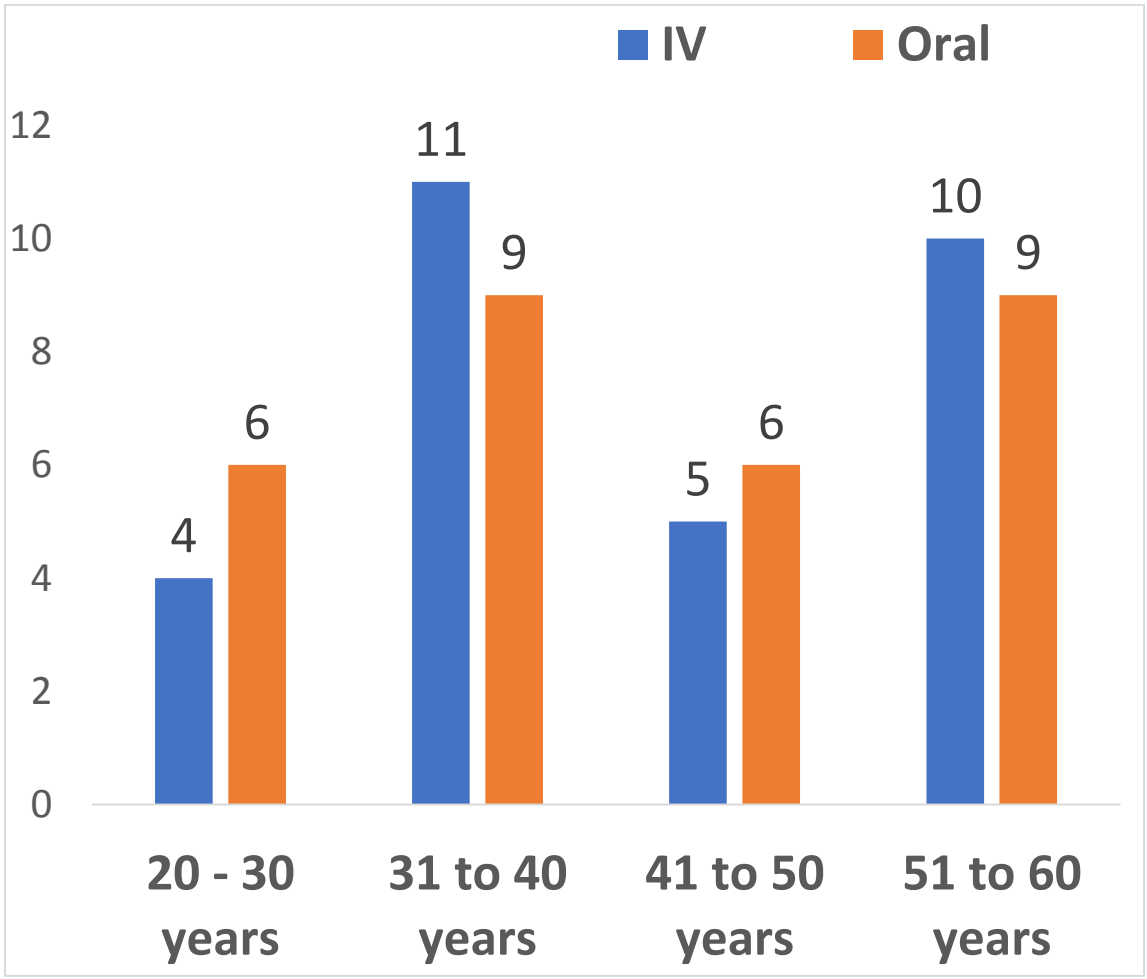


Table 2: Gender distribution of the study groups (n=60)

Group	Female n (%)	Male n (%)	Total n (%)
I.V Group	21 (70)	9 (30)	30 (50)
Oral Group	9 (30)	21 (70)	30 (50)
Total	30 (100)	30 (100)	60 (100)

Chi-square value: 9.600 p value: *0.002*

Comments:

The difference in gender distribution of subjects in the groups was statistically significant with I.V group having more females than oral group and vice-versa.

Fig 2: Gender distribution of the study groups (n=60)

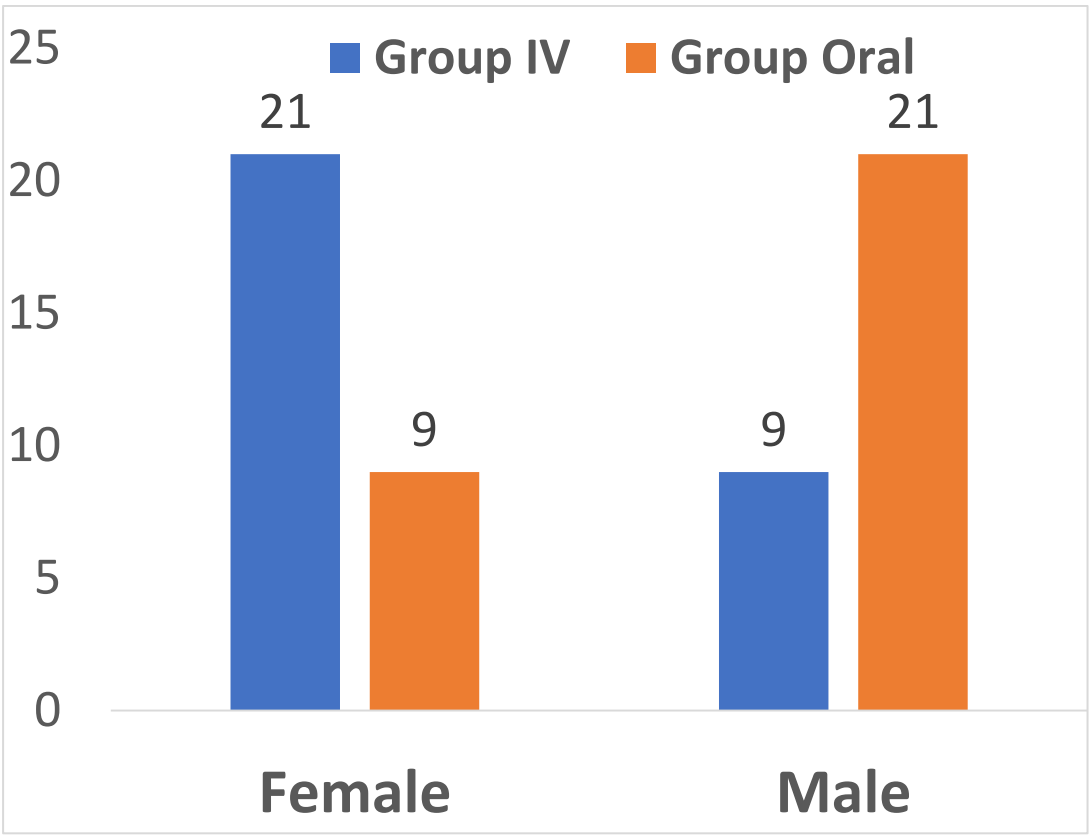


Table 3: Distribution of the subjects according to diagnosis (n=60)

Diagnosis	I.V Group n (%)	Oral Group n (%)	Total n (%)
Single valve disease	19 (63.3)	22 (73.3)	41 (68.3)
Double valve disease	11 (36.7)	7 (23.3)	18 (30)
Triple valve disease	0	1 (3.3)	1 (1.7)
Total	30 (100)	30 (100)	60 (100)

Chi-square value: 2.108 p value:0.348

Comments:

The difference in distribution of diagnosis based on number of valves involved between the groups was not statistically significant.

Fig 3: Distribution of the subjects according to diagnosis (n=60)

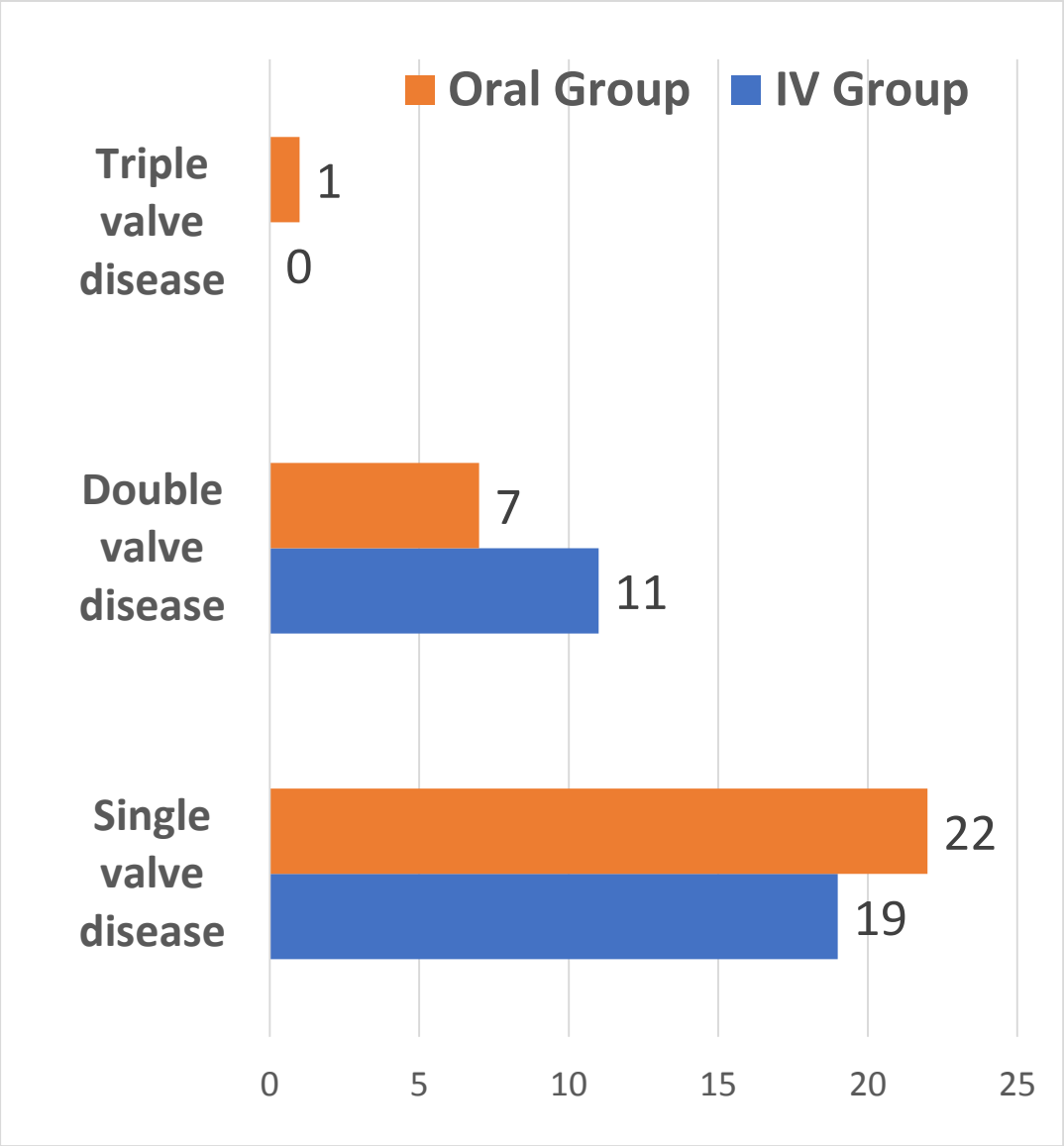


Table 4: Distribution of the subjects according to surgical procedure (n=60)

Procedure	I.V Group n (%)	Oral Group n (%)	Total n (%)
Aortic valve replacement (AVR)	7 (23.3)	10 (33.3)	17 (28.3)
Mitral valve replacement (MVR)	16 (53.3)	14 (46.7)	30 (50)
Double valve replacement (DVR)	2 (6.7)	4 (13.3)	6 (10)
Mitral valve replacement + Tricuspid annuloplasty (MVR + TRA)	4 (13.3)	2 (6.7)	6 (10)
Open Mitral Valvotomy (OMV)	1 (3.3)	0	1 (1.7)
Total	30 (100)	30 (100)	60 (100)

Chi-square value: 3.529 p value: 0.619

Comments: There was no statistically significant difference in proportion of various types of surgical procedures done between the two groups.

Fig 4: Distribution of the subjects according to surgical procedure (n=60)

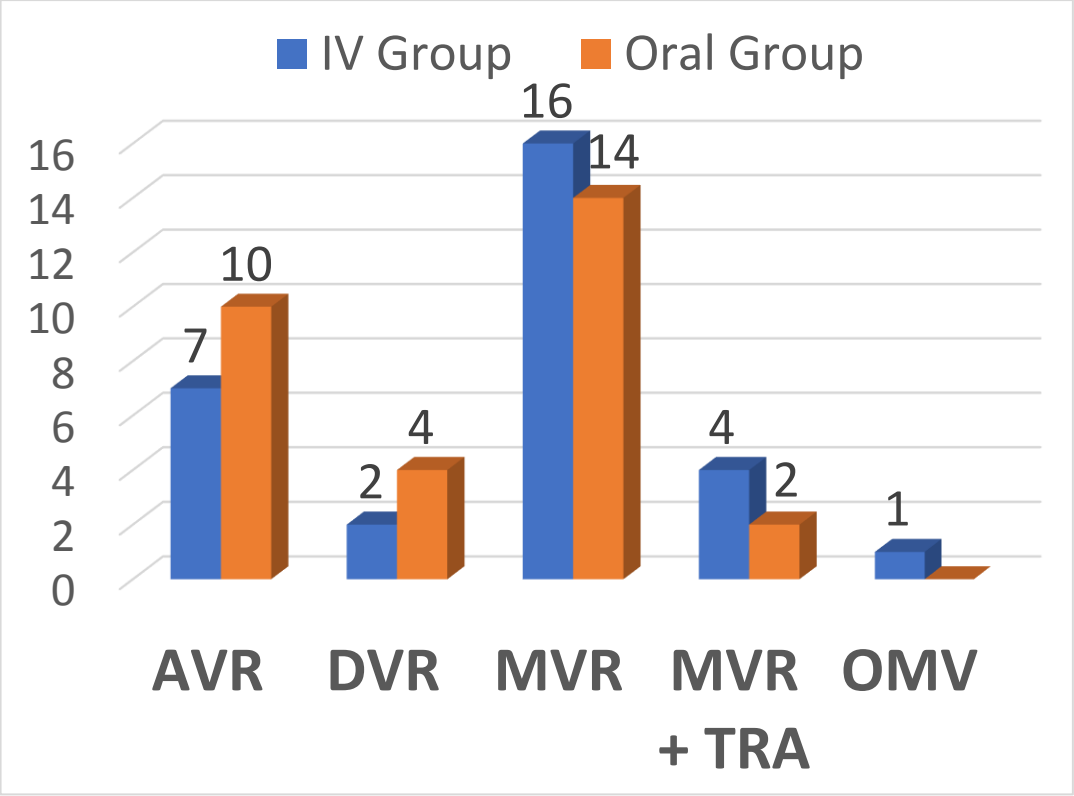


Table 5: Distribution of the study groups according to duration of surgical procedure (n=60)

Group	N	Mean duration (minutes)	Std. Deviation	Mean difference	Student 't' test p value	95% C.I
IV	30	249.0	52.348	-6.50	0.672	-37.10 to 24.10
Oral	30	255.5	65.355			

Comments:

The difference in duration of surgical procedure between subjects in the two groups was not statistically significant and hence the groups were comparable.

Fig 5: Distribution of the study groups according to duration of surgical procedure (n=60)

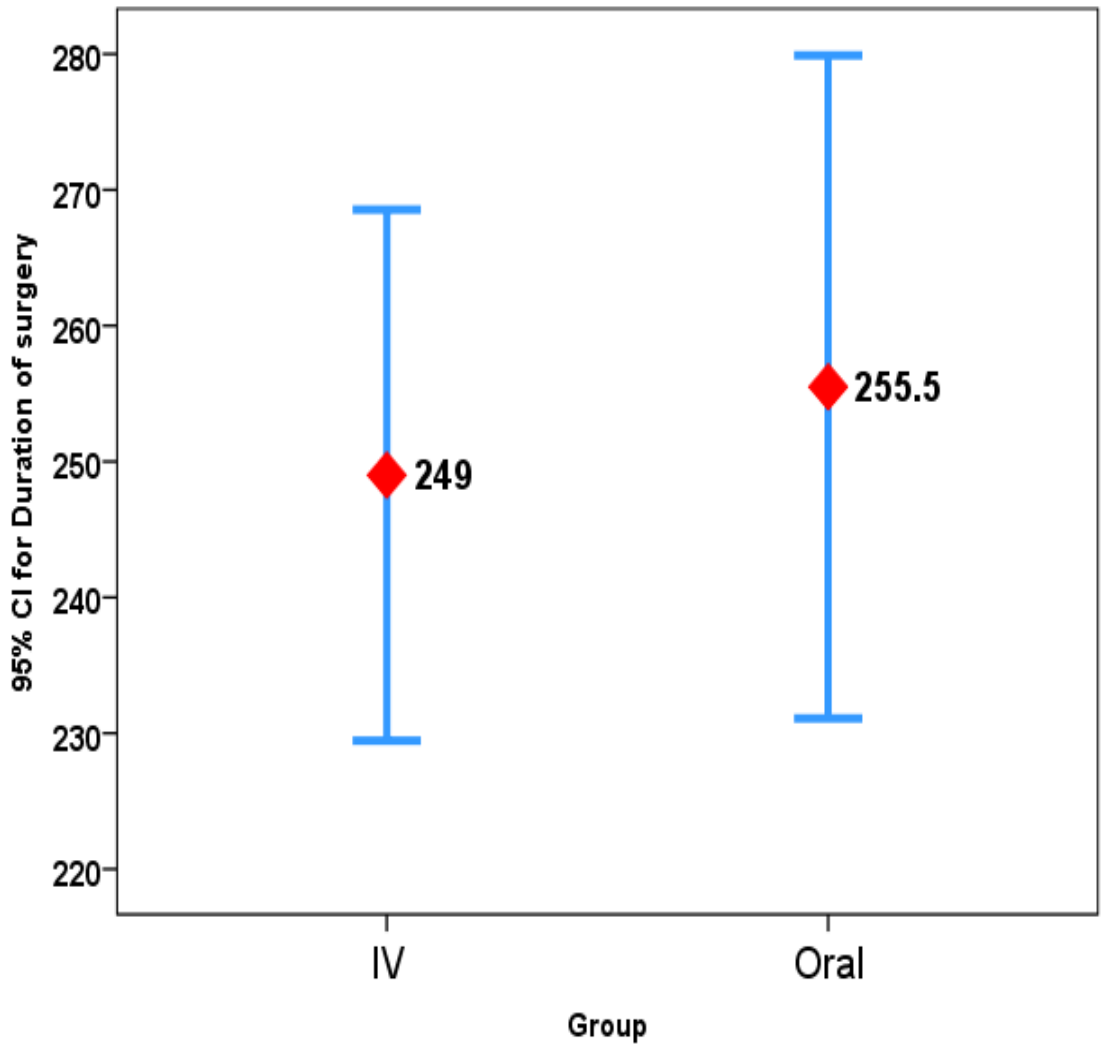


Table 6: Distribution of the study groups according to pre-operative (baseline) parameters (n=60)

Baseline Parameter	Group	Mean	Std. Deviation	Mean difference	Student 't'test p value
Hemoglobin (gm/dl)	IV	12.173	1.607	0.006	0.988
	Oral	12.167	1.725		
Platelet count (lakhs/ul)	IV	2.7030	0.8851	-0.087	0.679
	Oral	2.7903	0.7350		

Comments:

There was no statistically significant difference in baseline hemoglobin and platelet count levels between the two groups and hence the groups were comparable.

fig 6: Distribution of the study groups according to pre-operative (baseline) haemoglobin (n=60)

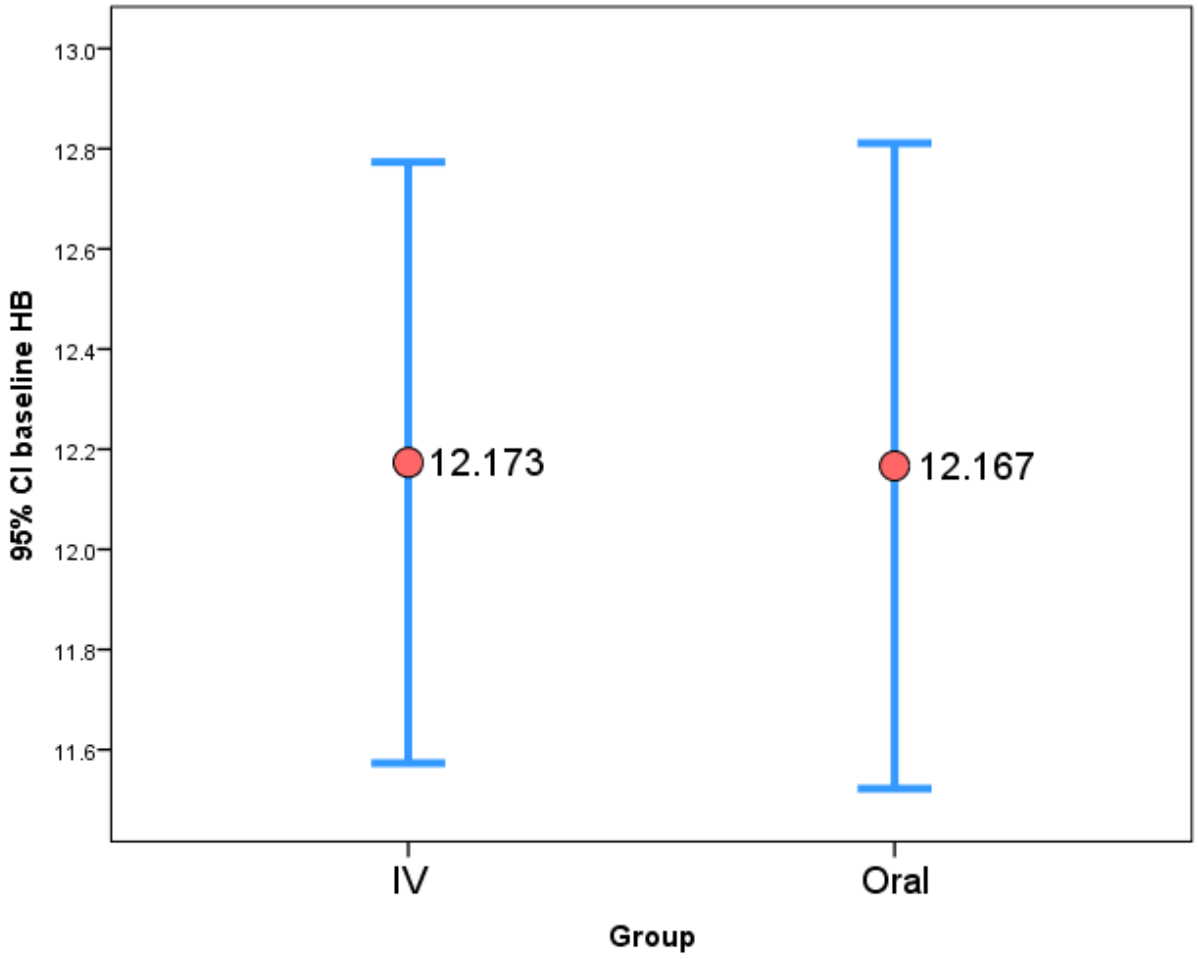


Table 7: Distribution of the study groups according to pre-operative (baseline) parameters (n=60)

Baseline Parameter	Group	Mean	Std. Deviation	Mean difference	Student 't' test p value
Activated clotting time	IV	157.57	34.473	17.80	***0.016***
	Oral	139.77	19.172		
Prothrombin time	IV	13.497	2.7339	-1.136	0.093
	Oral	14.633	2.4144		
INR	IV	1.0883	0.2256	-0.122	***0.026***
	Oral	1.2103	0.1868		
Bleeding Time	IV	132.13	8.27	-9.567	***0.012***
	Oral	141.70	18.41		
Clotting time	IV	245.33	48.54	-18.267	0.107
	Oral	263.60	37.16		

Comments:

1. There was no statistically significant difference in baseline prothrombin time and clotting time between the two groups.
2. The difference in baseline activated clotting time, INR and bleeding time between the two groups was statistically significant.

Fig 7: Distribution of the study groups according to pre-operative (baseline) platelet count (n=60)

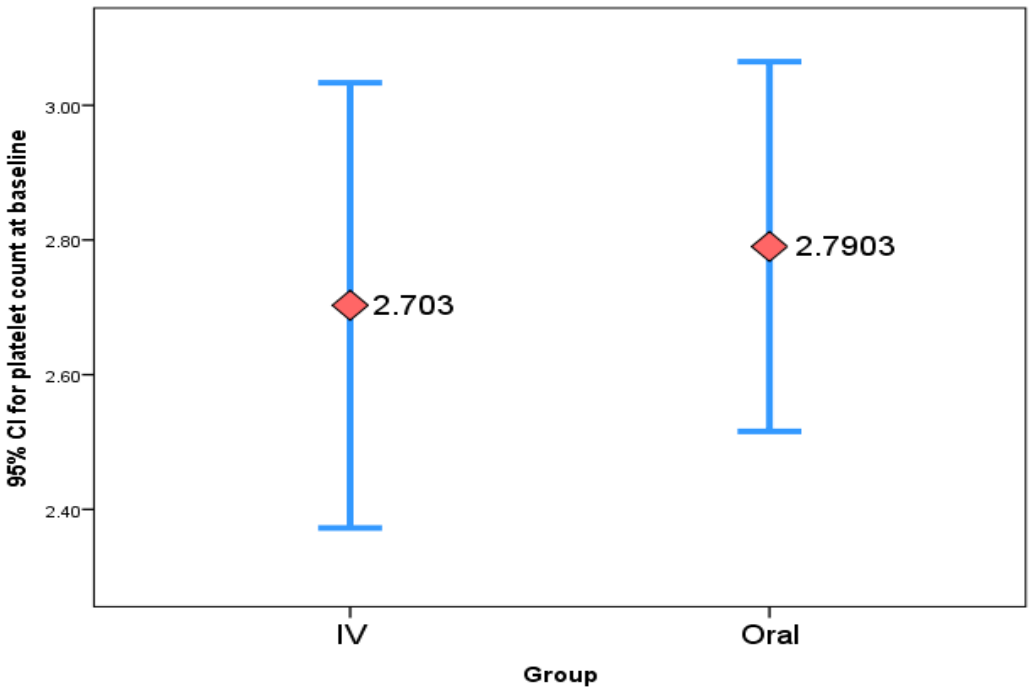


Table 8: Distribution of the study groups according to intra-operative blood loss (n=60)

Parameter	Group	Mean	Std. Deviation	Mean difference	Student 't'test p value
Intra-op blood loss (ml)	IV	678.33	286.08	-64.33	0.406
	Oral	742.67	308.48		

Comments:

There was no statistically significant difference in intra-operative blood loss between the two groups.

Fig 8: Distribution of the study groups according to pre-operative (baseline) parameters (n=60)

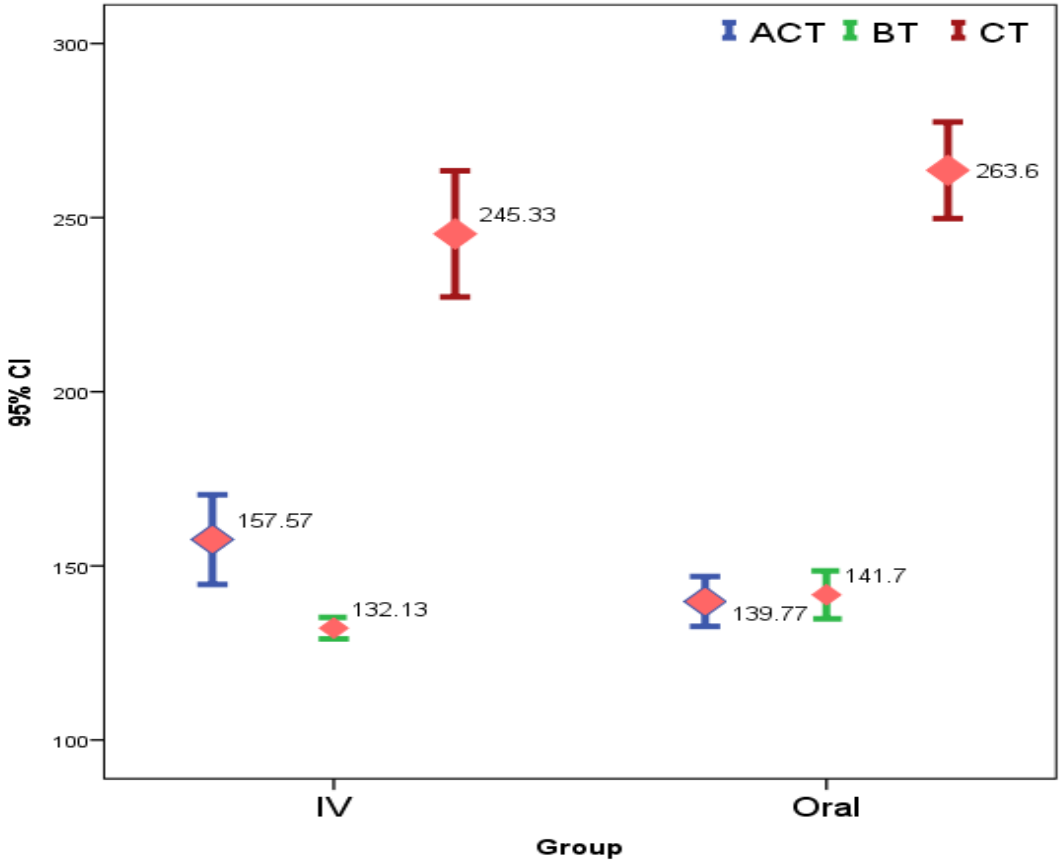


TABLE 9: DISTRIBUTION OF THE STUDY GROUPS ACCORDING TO INTRA-OPERATIVE ACTIVATED CLOTTING TIME (ACT) (N=60)

Parameter	Group	Mean	Std. Deviation	Mean difference	Student 't'test p value
Intra-op ACT	IV	160.70	29.038	2.633	0.711
	Oral	158.07	25.637		

Comments:

There was no statistically significant difference in intra-operative activated clotting time between the two groups.

Fig 9: Distribution of the study groups according to intra-operative blood loss in ml (n=60)

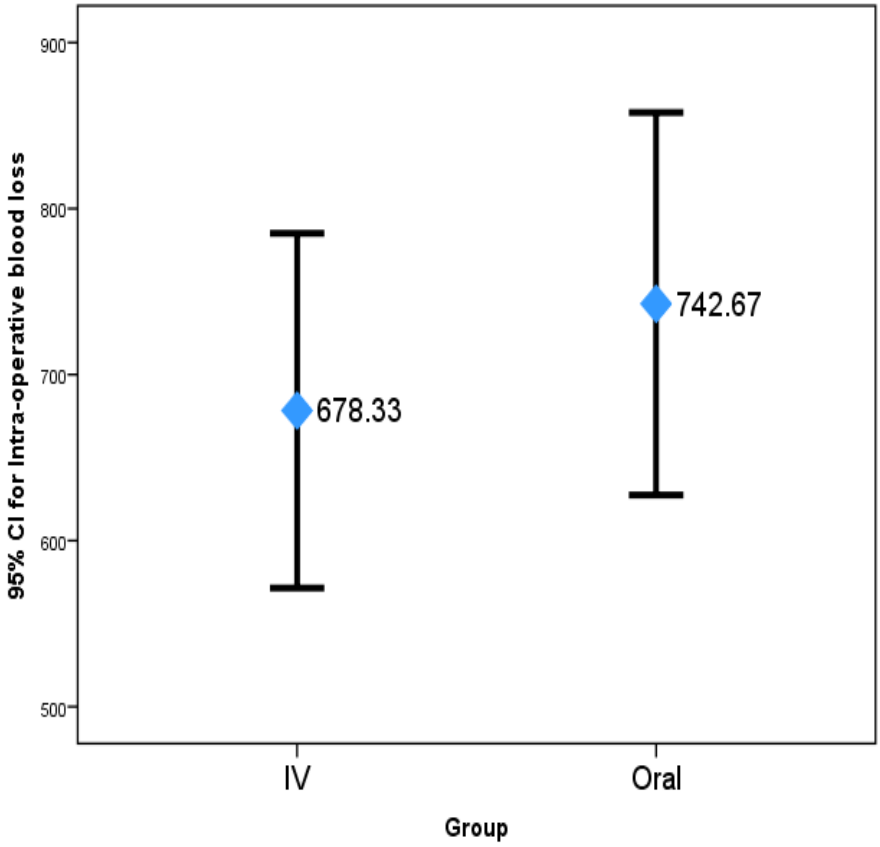


Table 10: Distribution of the study groups according to need for intra-operative blood transfusion (n=60)

Group	Blood transfusion		Total n (%)
	Not needed n (%)	Done n (%)	
I.V Group	13 (59.1)	17 (44.7)	30 (50)
Oral Group	9 (40.9)	21 (55.3)	30 (50)
Total	22 (100)	38 (100)	60 (100)

Chi-square value: 1.148 p value:0.284

Comments:

The difference in proportion of intra-operative blood transfusion between the groups was not statistically significant.

Fig 10: Distribution of the study groups according to need for intra-operative blood transfusion (n=60)

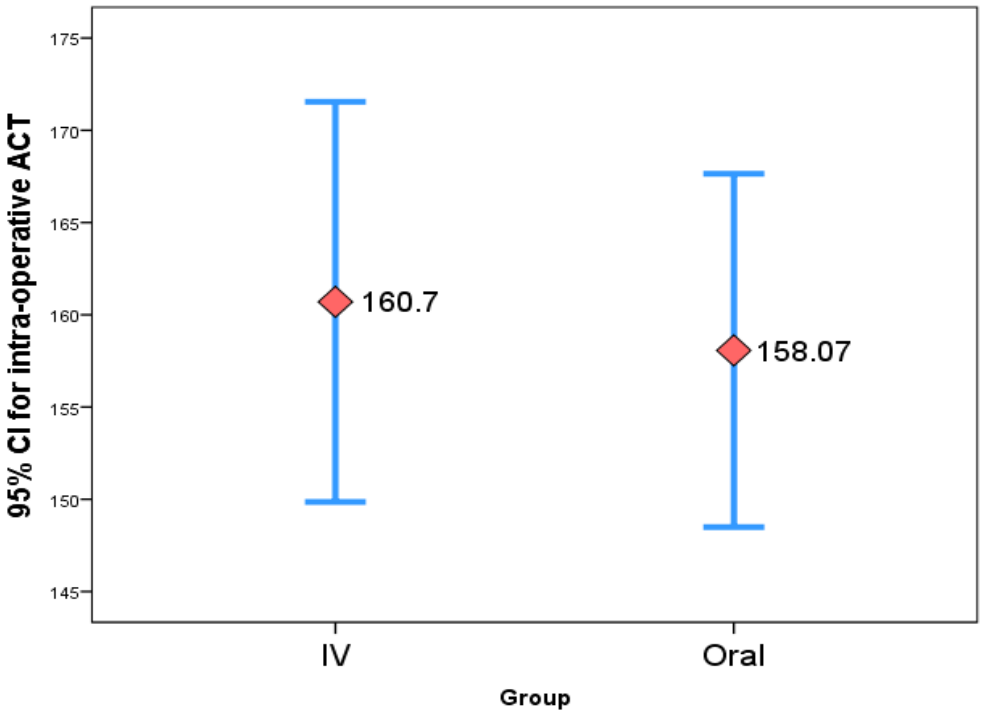


Table 11: Distribution of the study groups according to units of blood transfused in the intra-operative period (n=38)

Intra-op Parameter	Group	N	Mean	Median	IQR	Mann-Whitney test p value
Units of blood transfused	IV	17	1.29	1.0	1.0 to 2.0	*<0.001*
	Oral	21	2.57	2.0	2.0 to 4.0	

Comments:

Among the subjects who needed blood transfusion in the intra-operative period, subjects in the oral group required roughly 1 unit of blood product over and above the subjects in intra-venous group and this difference was statistically significant

Fig 11: Distribution of the study groups according to need for intra-operative blood transfusion (n=60)

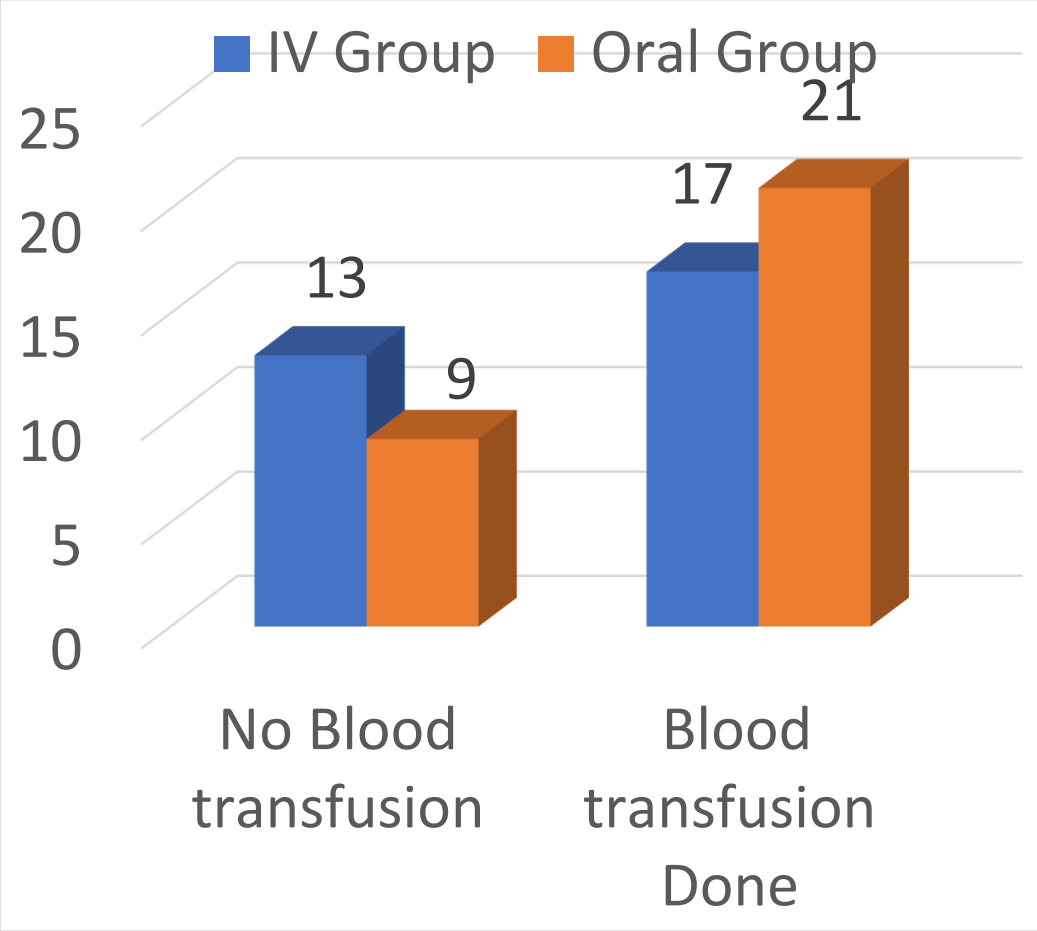


Table 12: Distribution of the study groups according to post-operative drain volume (n=60)

Parameter	Group	Mean	Std. Deviation	Mean difference	Student 't'test p value
Post-op drain volume (ml)	IV	362.00	188.577	-14.667	0.746
	Oral	376.67	159.056		

Comments:

There was no statistically significant difference in post-operative drain volume between the two groups.

Fig 12: Distribution of the study groups according to need for post - operative blood transfusion (n=60)

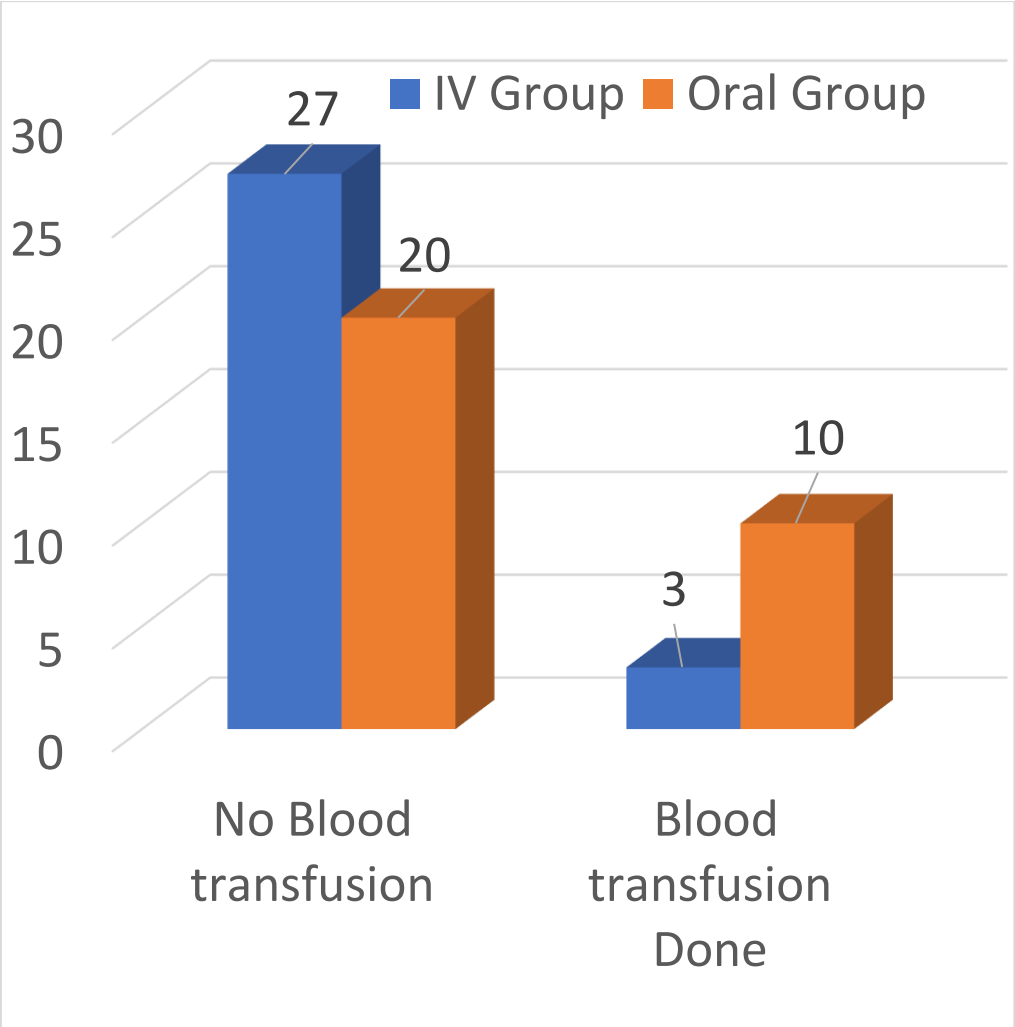


Table 13: Distribution of the study groups according to need for post-operative blood transfusion (n=60)

Group	Post-op Blood transfusion		Total n (%)
	Not needed n (%)	Done n (%)	
I.V Group	27 (57.4)	3 (23.1)	30 (50)
Oral Group	20 (42.6)	10 (76.9)	30 (50)
Total	47 (100)	13 (100)	60 (100)

Chi-square value: 4.812 p value*: 0.028*

Comments:

The difference in proportion of post-operative blood transfusion between the groups was statistically significant with more subjects in oral group requiring blood transfusion than the intra-venous group subjects.

Fig 13: Distribution of the study groups according to hemoglobin levels in the pre and post-operative period (n=60)

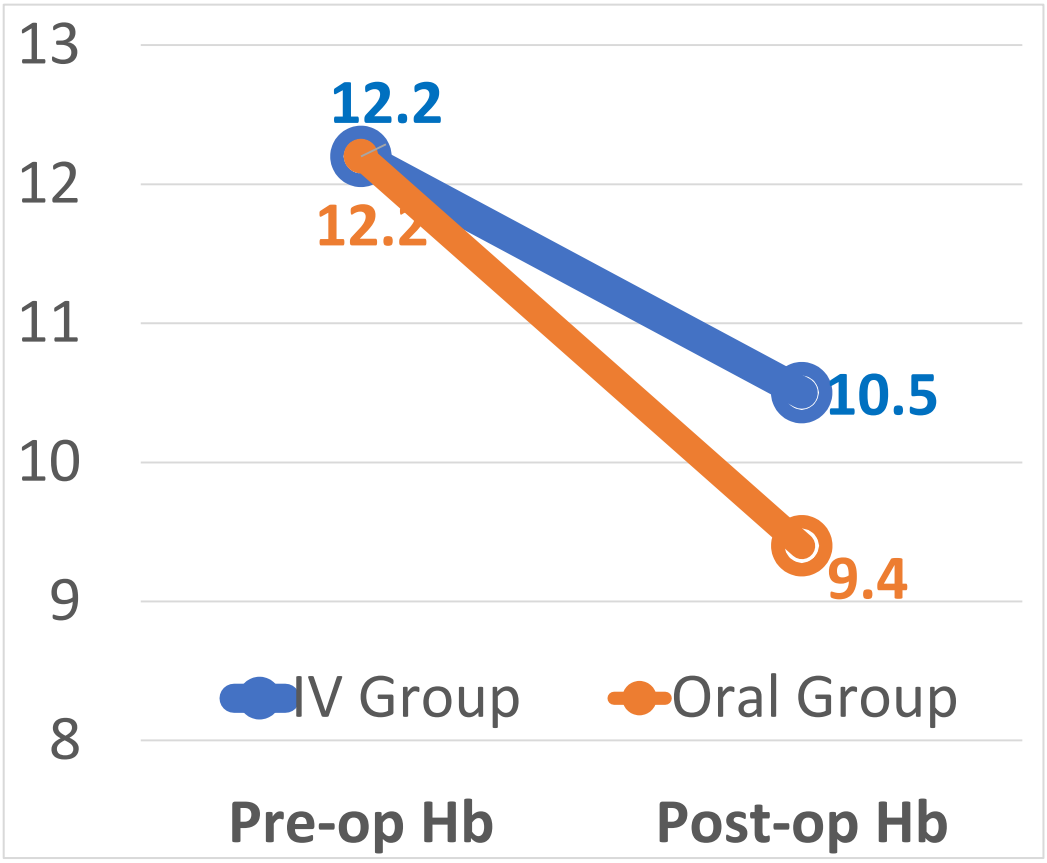


Table 14: Distribution of the study groups according to units of blood transfused in the post-operative period(n=13)

Post-op Parameter	Group	N	Mean	Median	IQR	Mann-Whitney test p value
Units of blood transfused	IV	3	1.33	1.0	1.0 to 2.0	0.232
	Oral	10	1.90	2.0	1.0 to 2.25	

Comments:

Among the subjects who needed blood transfusion in the post-operative period, subjects in the oral group required roughly 1 unit of blood product over and above the subjects in intra-venous group but this difference was not statistically significant.

Fig 14: Distribution of the study groups according to platelet levels in the pre and post-operative period (n=60)

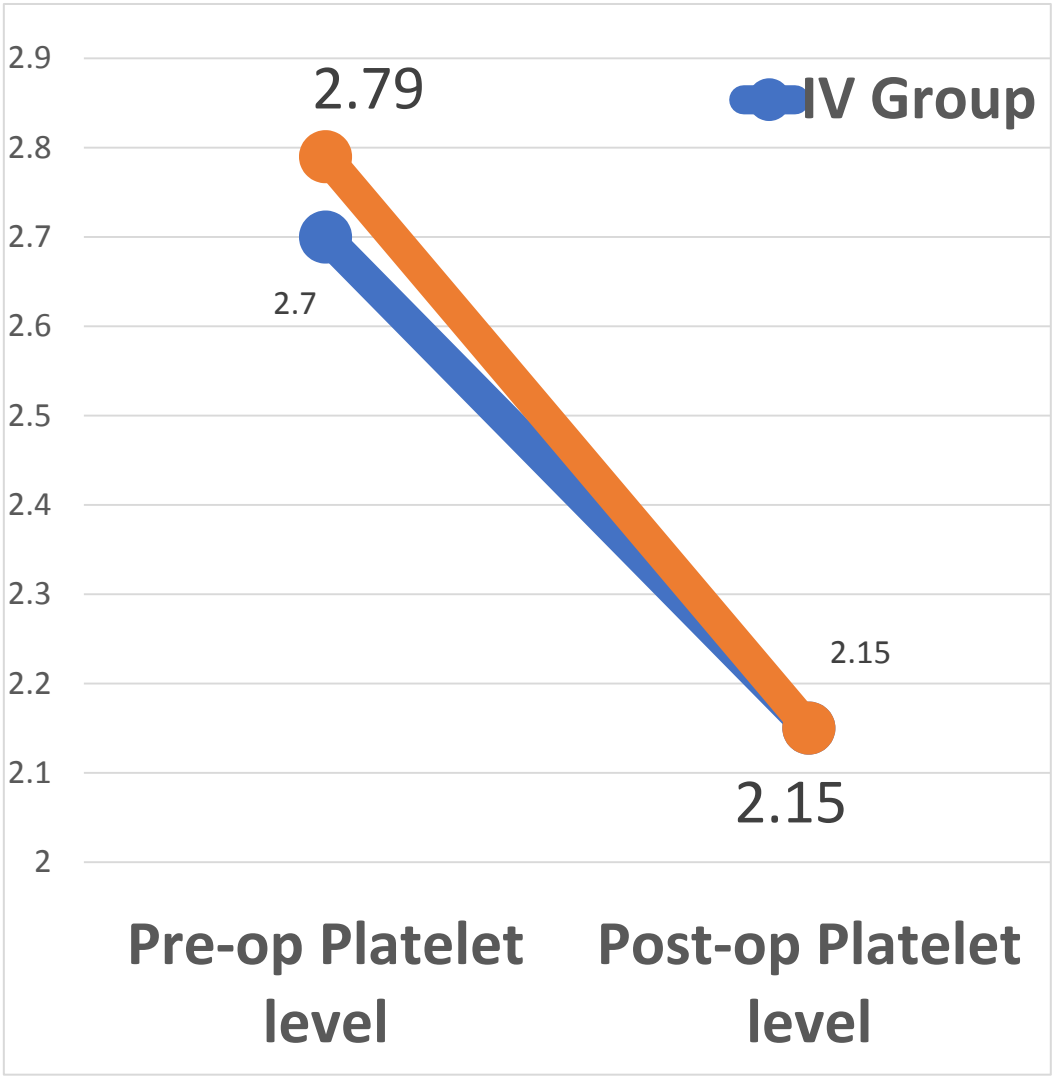


Table 15: Distribution of the study groups according to hemoglobin levels in the post-operative period (n=60)

Group	Mean Hb (g/dl)	Std. Deviation	95% Confidence Interval for Mean	
			Lower Bound	Upper Bound
I.V	10.503	1.8365	9.818	11.189
Oral	9.440	1.4373	8.903	9.977
Total	9.972	1.7207	9.527	10.416

ANCOVA test was applied to test the difference in mean hemoglobin levels in the post-operative period between the groups with baseline levels of hemoglobin as covariate.

ANCOVA test

Model	**Group**	**Hb changes + Group**
F statistic	**10.813**	**14.95**
Degree of freedom	**1,56**	**1,56**
p value	**0.002**	**0.001**

As there was statistically significant interaction in changes of Hb and the two groups, drop in Hb levels after surgery based on pre-surgery levels was analysed in each group separately.

Group	Post-op mean Hb fall (g/dl)	Std. Deviation	Mean difference	Student 't' test p value
I.V	1.670	0.6939	1.0567	0.001
Oral	2.727	1.5425		

Comments:

Student 't' test showed that there was statistically significant difference in mean fall of hemoglobin levels in the post-operative period with the hemoglobin fall being more in oral group than IV group.

Fig 15: Distribution of the study groups according to bleeding time in the pre and post-operative period (n=60)

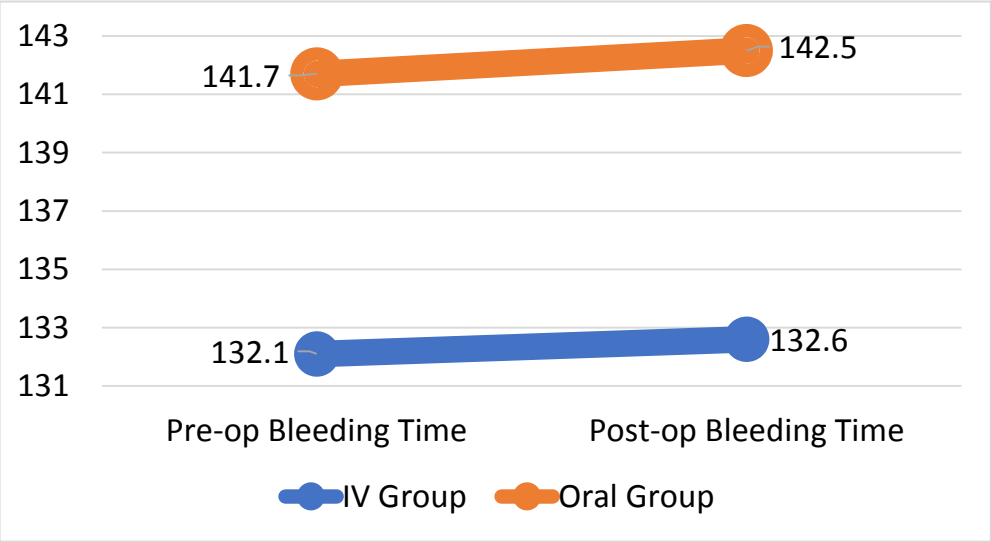


Table 16: Distribution of the study groups according to platelet levels in the post-operative period (n=60)

Group	Mean Platelet level (cells/µl)	Std. Deviation	95% Confidence Interval for Mean	
			Lower Bound	Upper Bound
I.V	2.1510	0.81883	1.8452	2.4568
Oral	2.1477	0.69483	1.8882	2.4071
Total	2.1493	0.75290	1.9548	2.3438

ANCOVA test was applied to test the difference in mean platelet levels in the post-operative period between the groups with baseline platelet levels in pre-operative period as covariate.

ANCOVA test

p value	0.289
F statistic	1.147
Degree of freedom	1,57

Comments:

ANCOVA test showed that there was no statistically significant difference in mean platelet levels in the post-operative period between the groups with baseline platelet levels in pre-operative period as covariate.

Fig 16: Distribution of the study groups according to clotting time in the pre and post-operative period (n=60)

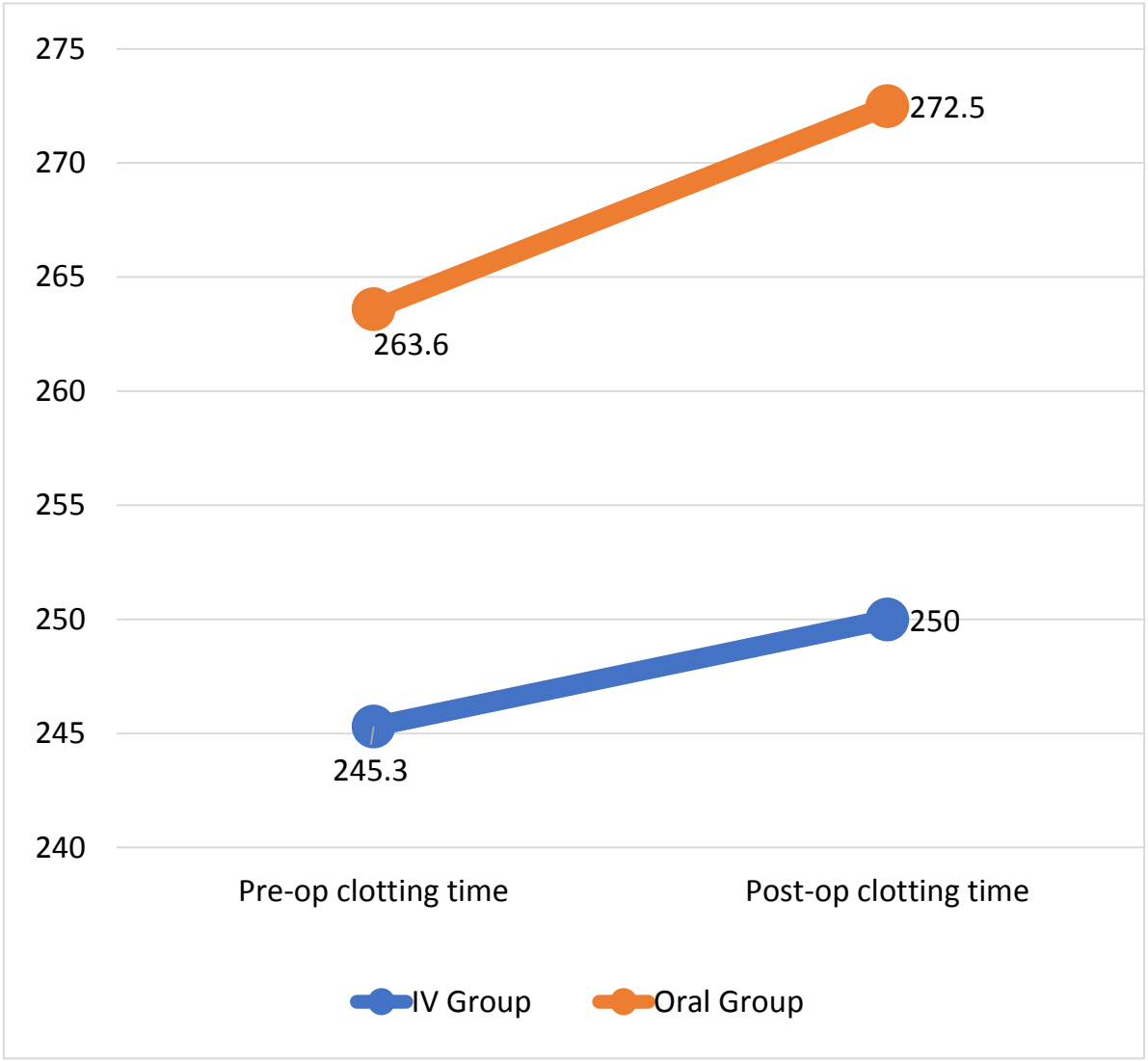


Table 17: Distribution of the study groups according to bleeding time in the post-operative period (n=60)

Group	Mean BT (seconds)	Std. Deviation	95% Confidence Interval for Mean	
			Lower Bound	Upper Bound
I.V	132.63	8.079	129.62	135.65
Oral	142.47	16.328	136.37	148.56
Total	137.55	13.701	134.01	141.09

ANCOVA test was applied to test the difference in mean bleeding time in the post-operative period between the groups with baseline bleeding time in pre-operative period as covariate.

ANCOVA test

p value	0.188
F statistic	1.779
Degree of freedom	1,57

Comments:

ANCOVA test showed that there was no statistically significant difference in mean bleeding time in the post-operative period between the groups with baseline bleeding time in pre-operative period as covariate.

Fig 17: Distribution of the study groups according to prothrombin time in the pre and post-operative period (n=60)

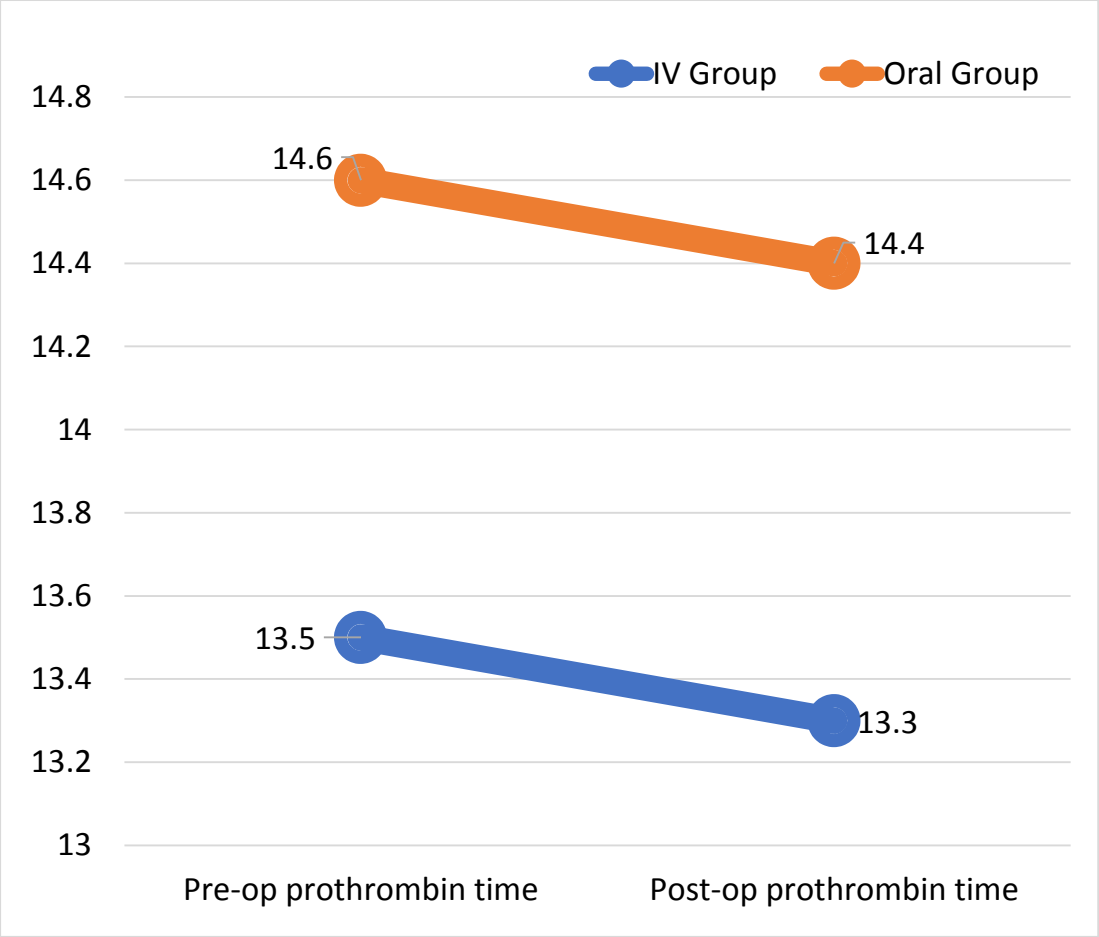


Table 18: Distribution of the study groups according to clotting time in the post-operative period (n=60)

Group	Mean CT (seconds)	Std. Deviation	95% Confidence Interval for Mean	
			Lower Bound	Upper Bound
I.V	250.00	41.206	234.61	265.39
Oral	272.50	41.098	257.15	287.85
Total	261.25	42.350	250.31	272.19

ANCOVA test was applied to test the difference in mean clotting time in the post-operative period between the groups with baseline clotting time in pre-operative period as covariate.

ANCOVA test

p value	0.181
F statistic	1.838
Degree of freedom	1,57

Comments:

ANCOVA test showed that there was no statistically significant difference in mean clotting time in the post-operative period between the groups with baseline clotting time in pre-operative period as covariate.

Fig 18: Distribution of the study groups according to INR in the pre and post-operative period (n=60)

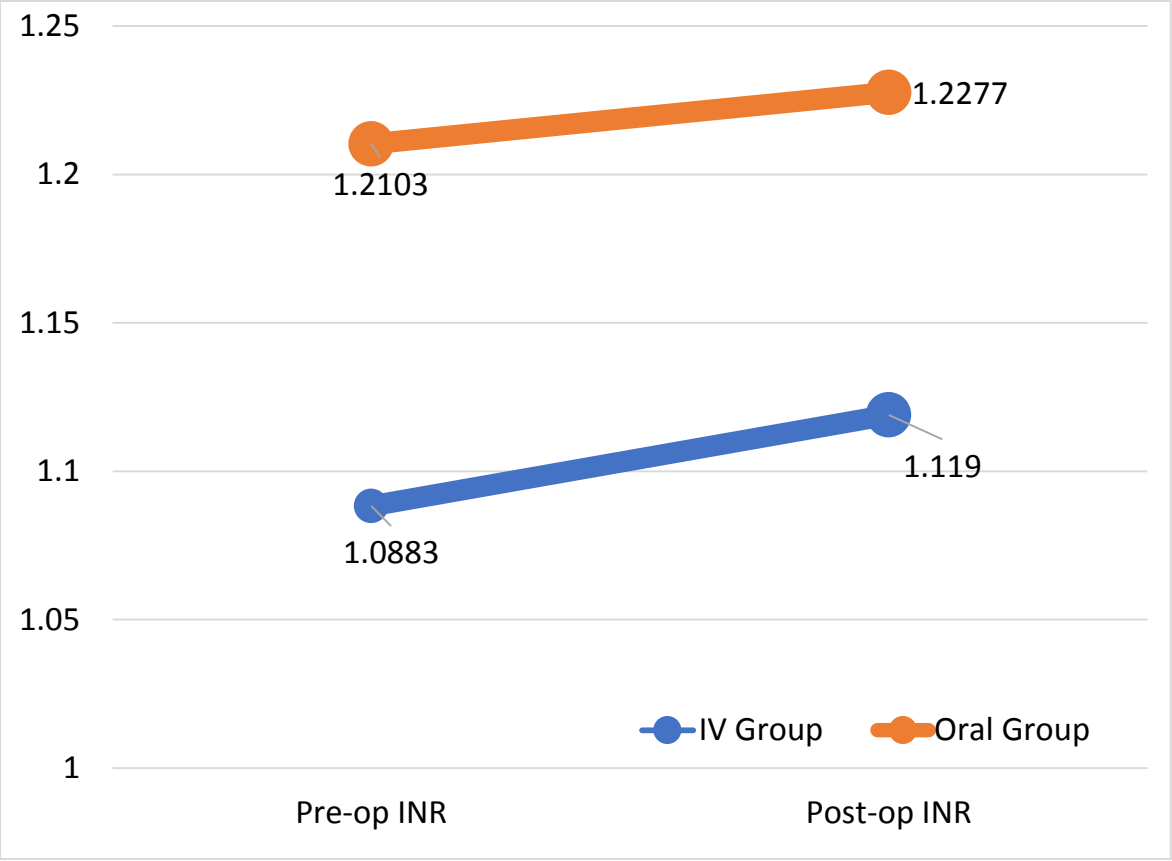


Table 19: Distribution of the study groups according to prothrombin time in the post-operative period (n=60)

Group	Mean PT (seconds)	Std. Deviation	95% Confidence Interval for Mean	
			Lower Bound	Upper Bound
I.V	13.330	2.2510	12.489	14.171
Oral	14.440	2.6479	13.451	15.429
Total	13.885	2.5000	13.239	14.531

ANCOVA test was applied to test the difference in mean prothrombin time in the post-operative period between the groups with baseline prothrombin time in pre-operative period as covariate.

ANCOVA test

p value	0.644
F statistic	0.216
Degree of freedom	1,57

Comments:

ANCOVA test showed that there was no statistically significant difference in mean prothrombin time in the post-operative period between the groups with baseline prothrombin time in pre-operative period as covariate.

Fig 19: Distribution of the study groups according to activated clotting time in the Pre, Intra and Post-operative period (n=60)

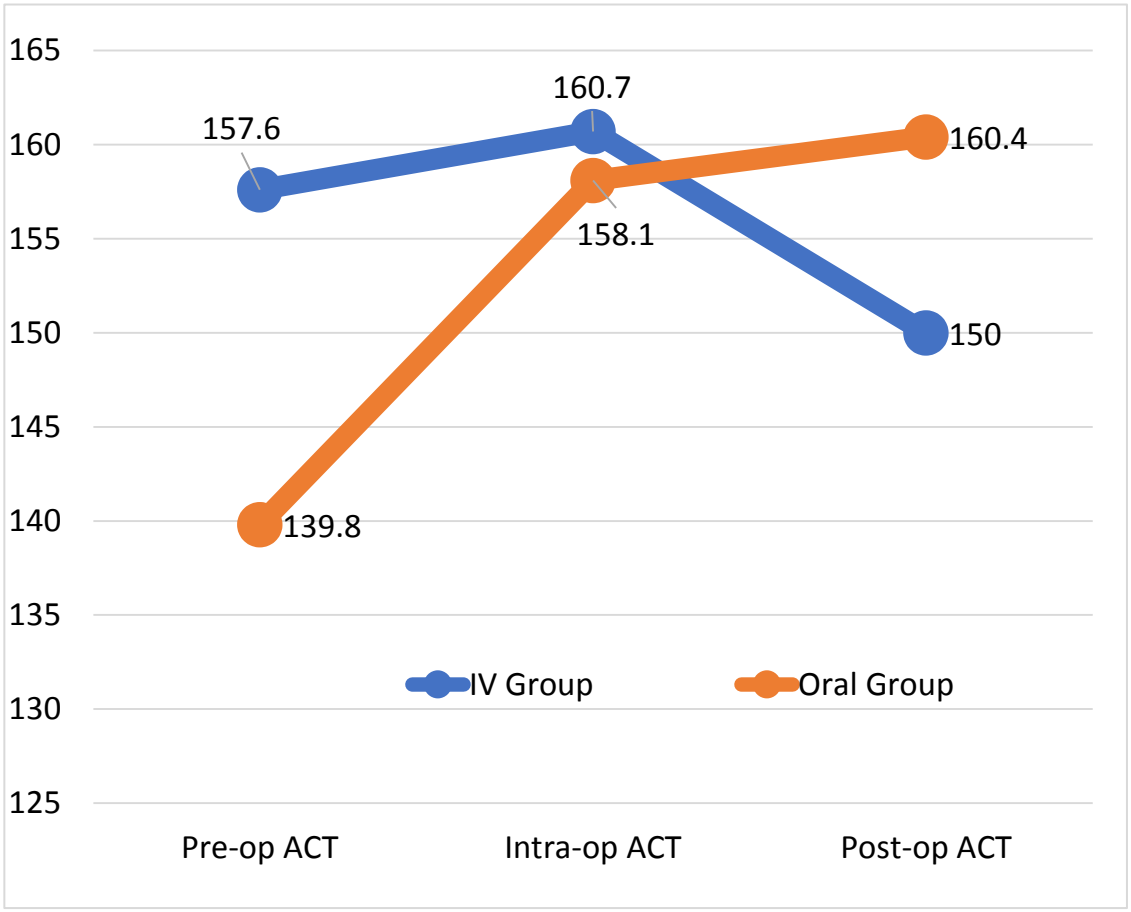


Table 20: Distribution of the study groups according to INR in the post-operative period (n=60)

Group	Mean INR	Std. Deviation	95% Confidence Interval for Mean	
			Lower Bound	Upper Bound
I.V	1.1190	.22293	1.0358	1.2022
Oral	1.2277	.21282	1.1482	1.3071
Total	1.1733	.22292	1.1157	1.2309

ANCOVA test was applied to test the difference in mean INR in the post-operative period between the groups with baseline INR in pre-operative period as covariate.

ANCOVA test

p value	0.723
F statistic	0.127
Degree of freedom	1,57

Comments:

ANCOVA test showed that there was no statistically significant difference in mean INR in the post-operative period between the groups with baseline INR in pre-operative period as covariate.

Fig 20: Comparison of need for intra-operative blood transfusion among subjects with surgery duration of above 5 hours (n=17)

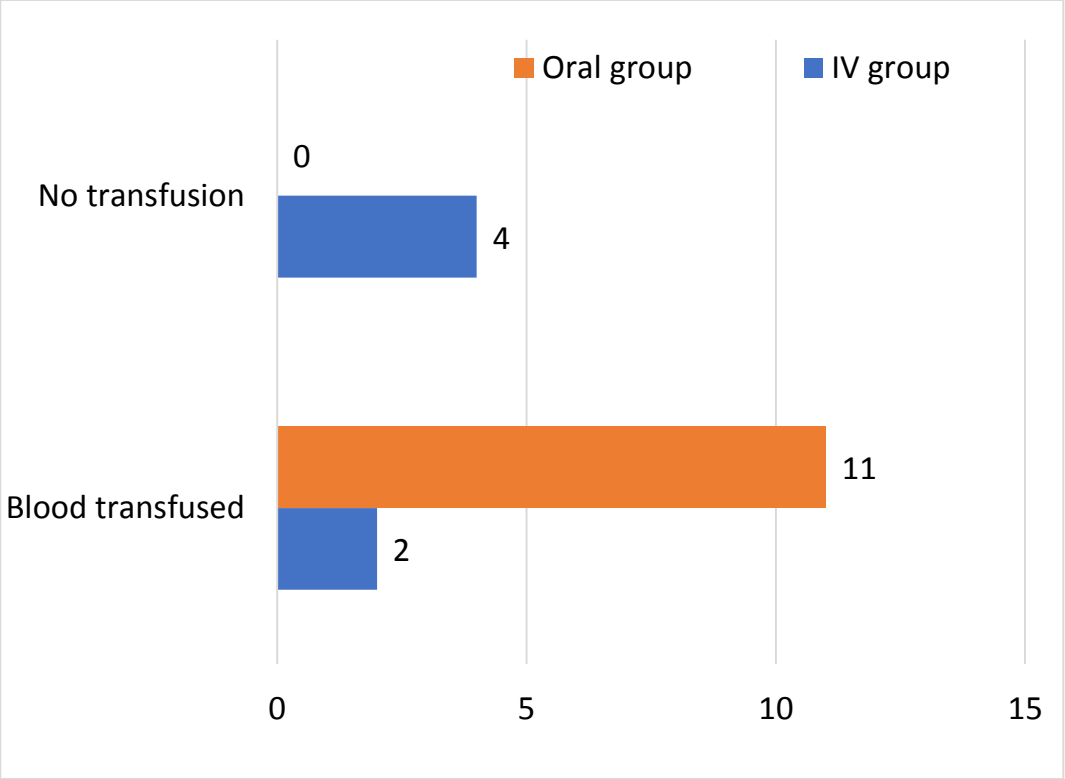


Table 21: Comparison of pre-operative and post-operative parameters in the IV group (n=30)

Parameter in IV group	Group	Mean	Std. Deviation	Mean difference	Paired 't' test p value
Hemoglobin	Pre-op	12.173	1.6071	1.67	**<0.001**
	Post-op	10.503	1.8365		
Platelet count	Pre-op	2.7030	.88514	0.55200	**<0.001**
	Post-op	2.1510	.81883		
Activated clotting time	Pre-op	157.57	34.473	7.533	0.271
	Post-op	150.03	13.116		
INR	Pre-op	1.0883	.22563	-0.03067	0.147
	Post-op	1.1190	.22293		
Prothrombin time	Pre-op	13.497	2.7339	0.1667	0.476
	Post-op	13.330	2.2510		
Bleeding Time	Pre-op	132.13	8.270	-0.500	0.530
	Post-op	132.63	8.079		
Clotting time	Pre-op	245.33	48.547	-4.667	0.381
	Post-op	250.00	41.206		

Comments:

1. There was no statistically significant difference between pre-operative and post-operative levels of Activated clotting time, prothrombin time, INR, Bleeding Time and clotting time in the IV group
2. However, the difference between pre-operative and post-operative levels of Hemoglobin and Platelet count among the subjects in IV group was statistically significant.

Fig 21: Comparison of need for post-operative blood transfusion among subjects with surgery duration of above 5 hours (n=17)

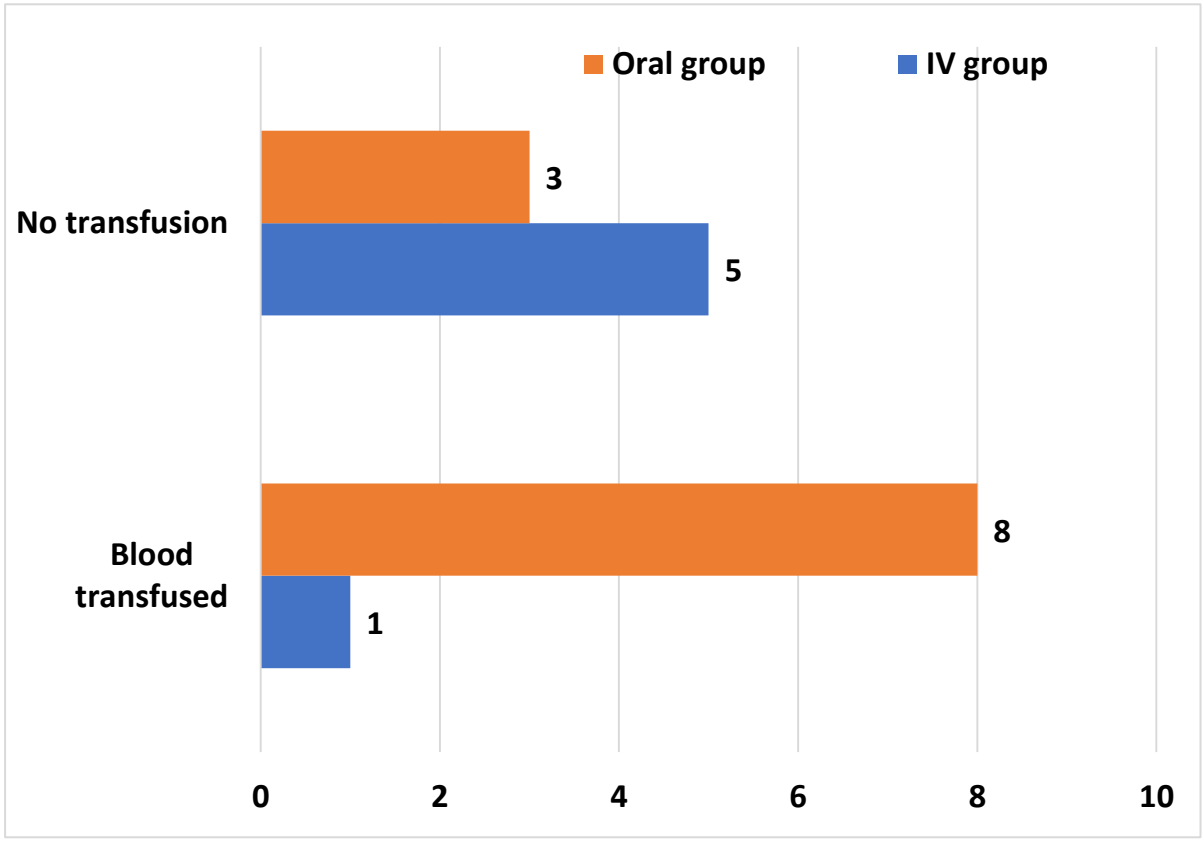


Table 22: Comparison of pre-operative and post-operative parameters in the oral group (n=30)

Parameter in Oral group	Group	Mean	Std. Deviation	Mean difference	Paired 't'test p value
Hemoglobin	Pre-op	12.167	1.7257	2.7267	***<0.001***
	Post-op	9.440	1.4373		
Platelet count	Pre-op	2.7903	.73509	0.64267	***<0.001***
	Post-op	2.1477	.69483		
Activated clotting time	Pre-op	139.77	19.172	-20.633	***<0.001***
	Post-op	160.40	10.711		
INR	Pre-op	1.2103	.18683	-0.01733	0.617
	Post-op	1.2277	.21282		
Prothrombin time	Pre-op	14.633	2.4144	0.1933	0.253
	Post-op	14.440	2.6479		
Bleeding Time	Pre-op	141.70	18.417	-0.767	0.664
	Post-op	142.47	16.328		
Clotting time	Pre-op	263.60	37.160	-8.900	***<0.001***
	Post-op	272.50	41.098		

Comments:

1. There was no statistically significant difference between pre-operative and post-operative levels of, prothrombin time, INR, and Bleeding Time in the oral group
2. However, the difference between pre-operative and post-operative levels of Haemoglobin, Platelet count, Activated clotting time and clotting time among the subjects in Oral group was statistically significant.

Table 23: Comparison of pre-operative, intra-operative and post-operative activated clotting time (n=60)

Activated clotting time	Group	Mean	Std. Deviation	N
Pre-op	IV	157.57	34.473	30
	Oral	139.77	19.172	30
	Total	148.67	29.075	60
Intra-op	IV	160.70	29.038	30
	Oral	158.07	25.637	30
	Total	159.38	27.189	60
Post-op	IV	150.03	13.116	30
	Oral	160.40	10.711	30
	Total	155.22	12.972	60

Repeated measures ANOVA was applied to test the difference in mean activated clotting time at various time intervals between the two groups.

Model	Changes in ACT over time	ACT changes + Group
Wilks's Lambda	2.198	7.609
p value	0.120	***0.001***

As there was statistically significant interaction in changes of ACT and the two groups, ACT levels at various time periods was analysed in each group separately.

Group	I.V	Oral
Wilks's Lambda	2.014	16.496
p value	0.152	<***0.001***
Partial Eta square	12.6%	54.1%

Post-Hoc Test for oral group (n=30)

Comparison Group	Mean difference	p value
Pre-op ACT vs Intra-op ACT	-18.30	***0.041***
Intra-op ACT vs Post-op ACT	-2.33	1.00
Pre-op ACT vs Post-op ACT	-20.63	<***0.001***

Comments:

1. Repeated measures ANOVA test showed that the changes in mean activated clotting time at various time intervals was statistically significant only in the oral group but not in the I.V group.
2. Post-hoc tests in the oral group revealed that rise in mean ACT in the intra-op and post-op period when compared to pre-op levels was statistically significant.

Table 24: Comparison of need for intra-operative blood transfusion among subjects with surgery duration of above 5 hours (n=17)

Group	Blood transfused n (%)	No transfusion n (%)	Total n (%)
IV group	2 (15.4)	4 (100)	6 (35.3)
Oral group	11 (84.6)	0	11 (64.7)
Total	13 (100)	4 (100)	17 (100)

Chi-square value: 6.242 p value:0.012

For volume of units transfused between 2 groups:

Mann Whitney U testp value: 0.102

Comments: The difference in distribution of intra-operative blood transfusion among subjects with surgery duration of above 5 hours was statistically significant with all the subjects in oral group Compared to one-third of the subjects in IV group requiring blood transfusion. But the number of units required among those who needed transfusion was not significant.

Table 25: Comparison of need for post-operative blood transfusion among subjects with surgery duration of above 5 hours (n=17)

Group	Blood transfused n (%)	No transfusion n (%)	Total n (%)
IV group	1 (11.1)	5 (62.5)	6 (35.3)
Oral group	8 (88.9)	3 (37.5)	11 (64.7)
Total	9 (100)	8 (100)	17 (100)

Chi-square value: 4.898 p value:0.027

For volume of units transfused between 2 groups:

Mann Whitney U testp value: 0.131

Comments:

The difference in distribution of post-operative blood transfusion among subjects with surgery duration of above 5 hours was statistically significant with more (89%) subjects in oral group requiring blood transfusion compared to 11% of the subjects in IV group. But the number of units required among those who needed transfusion was not significant.

Table 26: Comparison of pre-operative and post-operative hemoglobin levels among subjects with surgery duration of above 5 hours (n=17)

Group	Parameter	Mean Hb	Std. Deviation	Mean Hb drop	Paired 't'test p value
Oral group (n=11)	Pre-op Hb	11.527	1.4711	3.1091	<0.001
	Post-op Hb	8.418	1.2164		
IV group (n=6)	Pre-op Hb	12.550	1.9857	1.966	<0.001
	Post-op Hb	10.583	2.3319		

Comments:

There was a statistically significant difference (reduction) between pre-operative and post-operative levels of hemoglobin in both the groups.

Table 27: Comparison of reduction in hemoglobin levels among subjects with surgery duration of above 5 hours (n=17)

Group	N	Mean Hb reduction (preop-postop)	Std. Deviation	Mean difference in Hb drop	Student 't'test p value
Oral	11	3.109	0.8619	1.1424	0.012
IV	6	1.967	0.6022		

Comments:

There was a statistically significant difference between the two groups regarding the post-operative drop in Hemoglobin levels as the subjects in the oral group had roughly 1 gm greater reduction in hemoglobin in comparison to IV group.

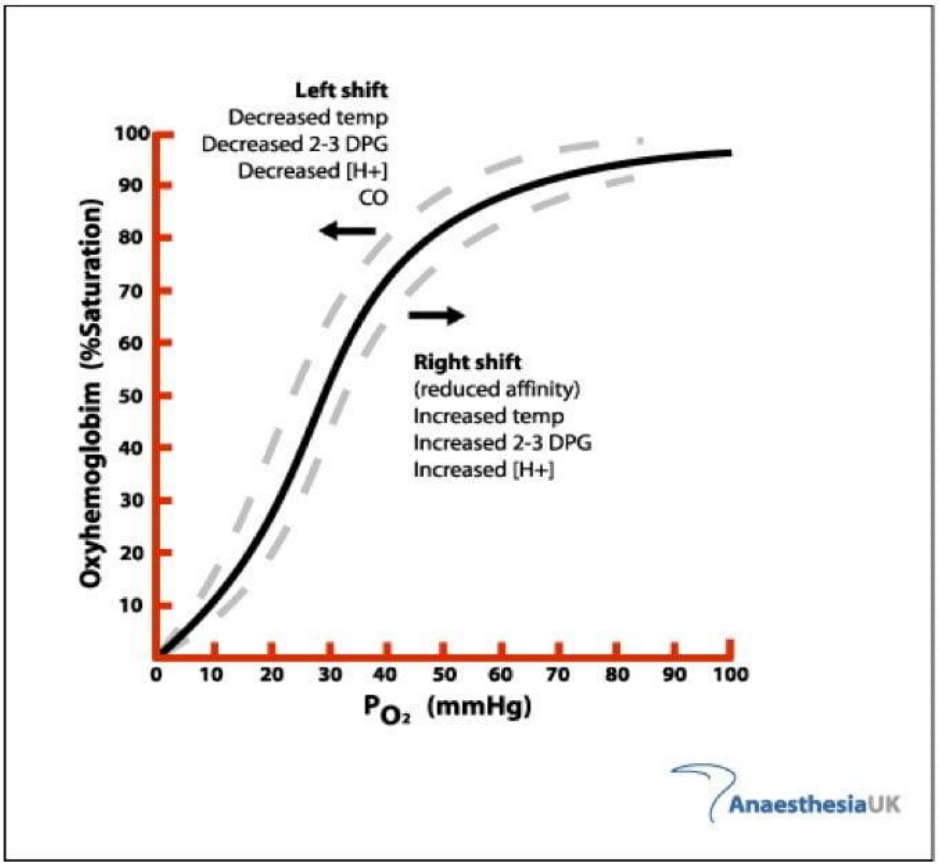
DISCUSSION

Blood loss is of main concern in major surgeries. The reason being anemia poses severe threat to life since hemoglobin is the main carrier of oxygen in blood.

Oxygen content = (Hb x 1.34 x SaO_2)+ (0.003 x PaO_2)

Decrease in oxygen content does not manifest initially till a critical level and this occurs because of the sigmoid shape of oxygen dissociation curve (cooperative binding of hemoglobin towards oxygen).

OXYGEN DISSOCIATION CURVE:



In a healthy individual, anemia is compensated by increasing the cardiac output to maintain the oxygen delivery to the tissues(oxygen flux).

Oxygen flux = cardiac output x oxygen content

Diseased heart would be unable to increase its output and hence would eventually fail. Thus, avoiding and treating anemia is of prime importance in cardiac patients. It can be done by either limiting the blood loss or by transfusing blood products.

Transfusing blood has its own demerits ranging from a mere febrile transfusion reaction, itching, rashes to a full blown anaphylaxis, TRALI (Transfusion Related Acute Lung Injury), blood borne infections which includes but not limited to malaria, HIV, Hepatitis B & C. Hence avoiding or limiting the amount of blood transfusions would be the ideal way to avoid the complications.

Then came the concept of blood conservation techniques. SABM (Society for Advanced Blood Management) team aims at using the latest drugs, technology & techniques to reduce and avoid the need for transfusions.

METHODS TO REDUCE BLOOD TRANSFUSIONS IN SURGERY:

- **PRE-OPERATIVE:**
    - In elective surgery- correct hemoglobin. Stop drugs interfering with hemostasis

- **INTRA OPERATIVE:**
    - Posture
    - Use vasoconstrictors
    - Torniquets
    - Antifibrinolytic drugs: Tranexamic acid
    - Controlled hypotension
- **POST OPERATIVE:**
    - Blood salvage techniques to reinfuse blood from drains.

Blood conservation techniques used nowadays include:

- Acute normovolemic hemodilution
- Hemodilution with crystalloid solution
- Intraop autologous donation
- Cell saver
- Apheresis/ platelet gel/ PRP
- Ultrafiltration (hemoconcentration), hemobag
- Autotransfusion of unprocessed shed blood from chest tube collection drain.

Cardiac surgeries involve dealing with heart and the major blood vessels. Thus, they have high potency for massive blood loss.

Fig. CARDIOPULMONARY BYPASS

Further, these patients are subjected to cardiopulmonary bypass wherein the blood is diverted out of the person's body, oxygenated and pumped back into the aorta from where it goes into the systemic circulation in a non-pulsatile fashion.

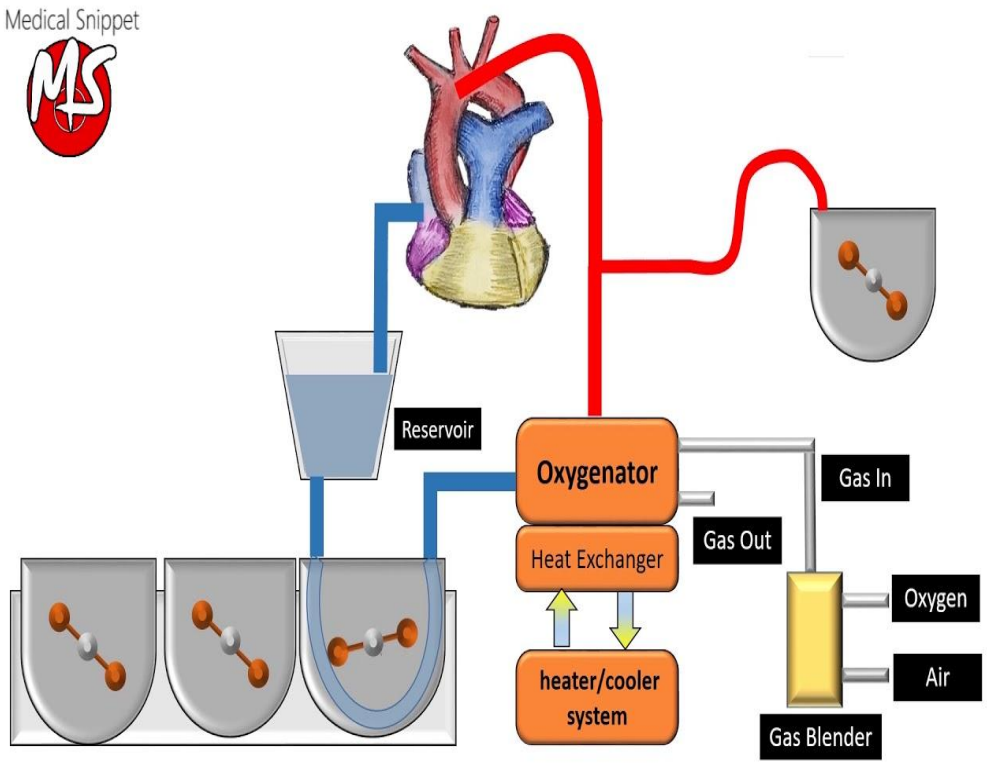


Fig. PRINCIPLES GOVERNING CARDIOPULMONARY BYPASS

Cardiopulmonary bypass has the following components and along with their clinical implications are enlisted as follows:

1. Pump consists of 2 roller head that compresses the tubings of bypass circuit. As it rotates, it propels fluid in the same direction as rotations while fluid is sucked behind the occlusive point.

The volume of fluid pumped out depends on:

- ✓ Volume of tubing occluded by the roller
- ✓ Number of revolutions made by the roller.

2. The pump has to be placed before membrane oxygenators because they are high resistant circuits and hence need higher force to push it through the oxygenator.

3. Occlusion setting in pump head is most important to reduce the hemolysis. It should be set at the maximum in cardioplegia and venting to avoid air entrainment.

4. The roller pumps are set at constant flow and hence they continue to deliver the set volume regardless of resistance. The line pressures have to be maintatined less than 250mmHg.

5. The circuit is primed with fluid before bypass. The concept of priming is:
    - To avoid gas embolism and
    - Perfusion improves when there is drop in viscosity
    - Reduced neurological, renal and pulmonary complications.

Prime volume is the volume required to de-air the circuit. And prime is the cause of hemodilution in CPB. This drop in viscosity increases the cardiac output. Thus the overall oxygen delivery to the tissues that we discussed earlier, may not be significantly affected even when the oxygen carrying capacity is reduced. Haemoglobin of 6-7g is considered reasonable in CPB.

Higher haemoglobin is justified when the patient has associated significant risk factors like Cerebro Vascular Accidents, Diabetes mellitus, cardiovascular diseases, carotid stenosis.

Predicted hematocrit = (patient blood volume x hematocrit) /
(patient blood volume + prime)

Patient's blood volume = 75 x weight (in kg)

Addition of crystalloid alone leads to drop in colloid oncotic pressure and hence tissue edema. Thus mannitol, albumin have been used along with the prime to avoid interstitial edema. Balanced lactated ringer is the most commonly used primer. An adult circuit needs around 1.5 to 2litres initially.

CLINICAL APPLICATION:

The blood is subjected to mechanical trauma in the rotors and hence there is potential space for mechanical damage to red blood cells and platelets. This may lead to increased blood loss postoperatively because of ineffective platelet plug formation. Furthermore there is dilution of blood because of addition of primer fluid of about 1 to 1.5litres. In our institute, tranexamic acid is used regularly for all open-heart surgeries to reduce blood loss. Tranexamic acid decreases fibrinolysis and hence helps form organized clot.

Ethamsylate helps reduce capillary bleeding especially when associated with plateletdysfunction. Ethamsylate was also thought to stabilise capillaries, reinforcing capillary membranes by polymerising hyaluronic acid[1]. Combination of tranexamic acid and ethamsylate have been used with good success in treating menorrhagia[2]. They have been testing in various surgeries including ENT, ophthalmic, urogenital, dental and general surgeries with positive results.

INFLAMMATORY MEDIATORS IN CARDIOPULMONARY BYPASS AND CLINICAL SIGNIFICANCE[29-32]:

Inflammation is the normal protective response of the body towards antigens or tissue injury. When this occurs in the body as a whole, it can lead to severe problems like:

- ★ Severe organ dysfunction
- ★ Post operative bleeding disorders
- ★ Respiratory distress syndrome
- ★ Death (rarely).

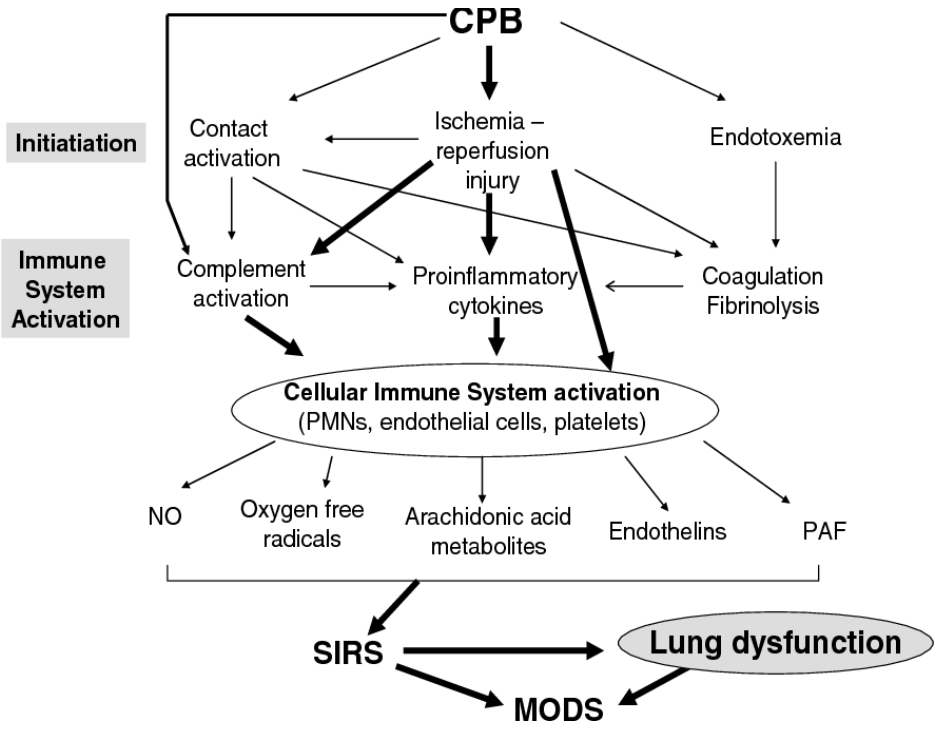
In cardiopulmonary bypass it is attributed to:

- ➢ blood interfacing with non-endothelial surfaces of the circuits of CPB
- ➢ Ischaemia and reperfusion following release of aortic cross clamp.

Inflammatory response consists of:

- Activation of complement system
- Activation of tissue macrophage and monocytes – releasing cytokines and other inflammatory mediators
- Activation of neutrophils and enzyme release.
- Leucocyte migration and accumulation in tissues
- Increased vascular permeability.

Cytokines are a class of chemoattractants synthesized by macrophages. Interleukins are a group of cytokines which produce inflammation by action on receptors of inflammatory cells and vasculature.



Following a extensive tissue injury, systemic inflammatory response is elicited. This manifests as fever, anorexia, synthesis of acute phase reactants. This response following a cardiac surgery is termed as “post perfusion syndrome”.

The inflammatory response to cardiopulmonary bypass influences the outcome as they bleed more, require respiratory support, have greater capillary leak.

In our study, Both the groups were comparable in terms of age, number of valves involved, proportion of the types of surgical procedures done and the duration of surgical procedure. There were more females in intravenous group than in oral group and this was statistically significant.

In the baseline parameters, hemoglobin, platelet counts, prothrombin time and clotting time were comparable while the difference in ACT, INR, and the bleeding time were statistically significant.

Intraoperative figures showed that the blood loss and the blood transfusions in both the groups were comparable. The ACT values were also comparable hence proving that both the drugs have very minimal to nil effects on the clotting parameters. Intraoperatively, Oral group needed transfusions required roughly 1 unit of blood product more than intravenous group and this was statistically significant.

Post operatively, the drain in both the groups were comparable.

There was a significant difference in transfusion requirements in both the groups with the oral group requiring roughly one blood product more than the intravenous group though the quantity was notstatistically significant. We could infer that the oral group requires either oral or IV supplementation post operatively to reduce the post op transfusion requirements.And when both these groups were compared with respect to duration > 5hours, all the subjects in oral group compared to one-third of the subjects in IV grouprequired blood transfusion. Hence, we conclude that with the passage of time oral group requires additional intravenous supplementation of drugs to prolong the effects.

ANCOVA test was applied to test the difference in mean hemoglobin, platelets, PT, INR bleeding time, and clotting time in the post-operative period between the groups with baseline levels as covariate.ANCOVA test showed that there was no statistically significant difference in mean platelet levels, PT, INR, bleeding time and clotting time in the post-operative period between the groups.

Student ‘t’ test showed that there was statistically significant difference in mean fall of hemoglobin levels in the post-operative period with the hemoglobin fall being more in oral group than IV group. And on comparing the reduction in hemoglobin levels among subjects with surgery duration of above 5 hours,there was a statistically significant reductionbetween pre-operative and post-operative levels of hemoglobin in both the groups.Further,

the subjects in the oral group had roughly 1 gm greater reduction in hemoglobin in comparison to IV group.

The difference in distribution of post-operative blood transfusion among subjects with surgery duration of above 5 hours was statistically significant with more (89%) subjects in oral group requiring blood transfusion compared to 11% of the subjects in IV group. But the number of units required among those who needed transfusion was not significant

SUMMARY

SUMMARY

This study was conducted to compare the efficacy of oral and intravenous formulations of tranexamic acid and ethamsylate combination in controlling bleeding in patients undergoing cardiopulmonary bypass.

The following results were obtained from our study:

The blood loss in both the groups were comparable.

The blood transfusions in both the groups were comparable.

The intra-operative ACT values were comparable hence proving that both the drugs have very minimal to nil drug interactions with heparin.

Intraoperatively, Oral group needed transfusions required roughly 1 unit of blood product more than intravenous group.

When groups were compared with respect to duration > 5hours, all the subjects in oral group compared to one-third of the subjects in IV group required blood transfusion. Hence, we conclude that oral group requires additional intravenous supplementation of drugs to prolong the effects when duration is more than 5hours.

Post operatively, in patients whose surgery duration of above 5 hours showed 89%subjects in oral group requiring blood transfusion compared to 11% of the subjects in IV group.

Statistically significant difference in mean fall of hemoglobin levels in the post-operative period with the hemoglobin fall being more in oral group than IV group.

On Comparing the reduction in hemoglobin levels among subjects with surgery duration of above 5 hours,there was a statistically significant reduction between pre-operative and post-operative levels of hemoglobin in both the groups with the oral group having roughly 1 gm greater reduction in hemoglobin in comparison to IV group.

There were no statistically significant difference in mean platelet levels, PT, INR, bleeding time and clotting time in the post-operative period in comparison with baseline between the groups and hence we can infer that there is almost nil effect on other bleeding or clotting parameters by both the drugs.

CONCLUSION

CONCLUSION

In conclusion, this study indicated that both intravenous and oral formulations of the combination were equally efficacious in controlling blood loss and decreasing the transfusion requirements in patients undergoing cardiopulmonary bypass, provided the duration of the surgery is within the plasma half life of the drugs.

In case of exceeding the plasma half life, additional doses or adopting methods like cell salvage methods may help reduce the blood loss and transfusions.

Oral formulation is found to be cost effective than intravenous formulation.

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ANNEXURES

ANNEXURES

PROFORMA

TITLE:

PROSPECTIVE RANDOMISED COMPARATIVE STUDY OF EFFICACY OF COMBINATION OF TRANEXAMIC ACID AND ETHAMSYLATE BY ORAL AND INTRAVENOUS ROUTES IN RELATION TO CONTROL OF BLEEDING IN CARDIAC SURGERIES.

DATE: IP NO:

NAME:

AGE: SEX:

DIAGNOSIS:

SURGICAL PROCEDURE:

Ht: CVS:

Wt: RS:

PRE OP ASSESSMENT: HB: BT/CT:

AIRWAY: PLATELET COUNT:

ACT:

HISTORY:

Any Co-morbid illness

H/O Documented Difficult Airway

H/O previous surgeries

INFORMED CONSENT IN TAMIL:

RANDOMIZATION: Tick the following

1) GROUP O

2) GROUP I

IV line

PREMEDICATION

MONITORS

BASELINE VITAL PARAMETERS

Heart rate	
IBP	
SpO2	
Hb	

MEASURES OF PRIMARY OUTCOME AND SECONDARY OUTCOME

INTRA –OPERATIVE

- Heart Rate

- Non-invasive BP, Invasive BP.
- SPO2
- Respiratory rate
- Central venous pressure
- Volume of blood collected in suction apparatus
- Partial/complete blood soaked gauze counts(3 / 5ml)
- Partial / complete blood soaked pads counts (30 / 50 ml)
- Change in hematocrit after surgery
- Change in BT, CT, platelet count after surgery
- HR, BP, SpO2, Urine output
- Postoperative drain collected

END OF SURGERY:

ACT	**No of Soaked Pads**	**No. of Soaked Gauze**	**Suction Collection**	**Blood Transfusion (Yes / No)**

POST OP BLOOD LOSS ASSESSMENT (24HRS AFTER SURGERY)

Suction Drain	Blood Transfusion	Hematocrit	BT / CT	Platelet Count

INFORMATION TO PARTICIPANTS

Investigator **:** Dr HEMALATHA R V

Name of the Participant:

Title:

"**PROSPECTIVE RANDOMISED COMPARATIVE STUDY OF EFFICACY OF COMBINATION OF TRANEXAMIC ACID AND ETHAMSYLATE BY ORAL AND INTRAVENOUS ROUTES IN RELATION TO CONTROL OF BLEEDING IN CARDIAC SURGERIES."**

You are invited to take part in this research study. We have got approval from the Institutional Ethical Committee. You are asked to participate because you satisfy the eligibility criteria. We want to compare between oral and intravenous formulations of tranexamic acid and ethamsylate and study their effectiveness in reducing intra op and postoperative blood loss in patients undergoing cardiac valve replacement surgeries.

What is the Purpose of the Research:

To know the effect of tranexamic acid in reducing intraoperative and postoperative blood loss in patients undergoing cardiac valve replacement surgeries.

The secondary purpose of the study is

1. To know the requirement of transfusion intra-operatively and post - operatively.
2. To study the effect of drug on hematocrit change after surgery.

The Study Design:

Total number of patients 60. All undergoing cardiac valve replacement surgeries.

Group 1- Group- O - Oral ethamsylate and Oral tranexamic acid**.**

Group2-Group- I - Intravenous ethamsylate and Intravenous tranexamic acid.

Benefits:

★ Intra operative and post operative blood loss reduction.

★ Decreased transfusion requirements and transfusion related hazards.

Discomforts and risks:

★ Allergy to tranexamic acid and ethamsylate.

This intervention has been shown to be well tolerated as shown by previous studies. And if you do not want to participate you will have an alternative setting of the standard treatment and your safety is our prime concern.

Time :

Date : Signature / Thumb Impression of the patient

Place :

Patient Name:

Signature of the Investigator : _____

Name of the Investigator : _____

PATIENT CONSENT FORM

Study title :

PROSPECTIVE RANDOMISED COMPARATIVE STUDY OF EFFICACY OF COMBINATION OF TRANEXAMIC ACID AND ETHAMSYLATE BY ORAL AND INTRAVENOUS ROUTES IN RELATION TO CONTROL OF BLEEDING IN CARDIAC SURGERIES."

Study centre :

Institute of Anaesthesiology and Critical Care,

Rajiv Gandhi Govt. General Hospital,

Madras Medical College,

Chennai- 600003

Participant name: **I.P. No:** **Age:** **Sex:**

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I have been explained about the pitfalls in the procedure. I have been explained about the safety, advantage and disadvantage of the technique.

I understand that my participation in the study is voluntary and that I am free to withdraw at anytime without giving any reason.

I understand that my identity will not be revealed in any information released to any third party or published, unless as required under the law . I agree not to restrict the use of any data or results that arise from the study. I hereby give permission to undergo complete clinical examination and diagnostic tests including haematological, biochemical, radiological tests.

I hereby agree to participate in this study.

Time:

Date: Signature/thumb impression of patient

Place: Patient name:

Signature of the investigator:

Name of the investigator:

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு :

இதய அறுவை சிகிச்சையின் போது ஏற்படும் இரத்த கசிவை கட்டுப்பத்துவதில் டிரானக்ஸாமிக் ஆசிட் மற்றும் இதாம்ஸைலேட் மருந்துகளின் செயல்திறன் வாய்வழி மற்றும் இரத்தக் குழாய் வழி செலுத்தி ஒப்பிட்டறிதல்.

ஆராய்ச்சி நிலையம் : மயக்கவியல் துறை,
இராஜீவ் காந்தி அரசு பொது மருத்துவமனை மற்றும்
சென்னை மருத்துவக் கல்லூரி,
சென்னை - 600 003.

பங்கு பெறுபவரின் பெயர் : உறவுமுறை :

பங்கு பெறுபவரின் எண். :

பங்கு பெறுபவர் இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களைப் பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்ஆய்வில் தன்னிச்சையாகத்தான் பங்கேற்கிறேன். எந்தக் காரணத்தினாலோ எந்தக் கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்ஆய்வில் இருந்து விலகிக் கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்மந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும்போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளைப் பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக் கொள்ளவும் அதைப் பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்குக் கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன், இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன். ☐

பங்கேற்பவரின் கையொப்பம்..... இடம்..... தேதி
கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம்.....

ஆய்வாளரின் கையொப்பம்..... இடம்..... தேதி

ஆய்வாளரின் பெயர்.....

பக்க விளைவுகள்:

டிரனக்ஸாமிக் ஆசிட் மற்றும் இதாம்ஸைலேட் மருந்திற்கு ஒவ்வாமை ஏற்படலாம்.

இவ்வாய்வு முந்தைய ஆய்வுகளால் பாதுகாப்பானதாக குறிப்பிடப்பட்டுள்ளது. தங்களுக்கு விருப்பமில்லாவிட்டால் வழக்கமான சிகிச்சை தொடர்ந்து அளிக்கப்படும். தங்களின் பாதுகாப்பே எங்களின் நோக்கம்.

ஆய்வாளரின் பெயர்

பங்குகொள்பவரின் /
பாதுகாவலரின் பெயர்

ஆய்வாளரின் கையொப்பம்

பங்குபெறுபவரின்
கையொப்பம் /கட்டை விரல் ரேகை

ஆராய்ச்சி தகவல் தாள்

ஆய்வாளர் பெயர் :

பங்கேற்பாளர் பெயர் :

ஆராய்ச்சி தலைப்பு :

இதய அறுவை சிகிச்சையின் போது ஏற்படும் இரத்த கசிவை கட்டுப்பத்துவதில் டிரானக்ஸாமிக் ஆசிட் மற்றும் இதாம்ஸைலேட் மருந்துகளின் செயல்திறன் வாய்வழி மற்றும் இரத்தக் குழாய் வழி செலுத்தி ஒப்பிட்டறிதல்.

இந்த ஆய்வு நடத்த துறை சார்ந்த வல்லுநர்களின் கூட்டத்திடமிருந்து அனுமதி பெறப்பட்டுள்ளது. இவ்வாய்வில் பங்குபெற நிர்ணயிக்கப்பட்ட தகுதி வரம்பிற்குள் தாங்கள் வருவதால், ஆய்வில் பங்குபெற தங்களை வேண்டுகிறோம்.

இவ்வாய்வின் பயன்கள்:

இதய அறுவை சிகிச்சையின் போது ஏற்படும் இரத்த கசிவை கட்டுப்படுத்துவதில் டிரனக்ஸாமிக் ஆசிட் மற்றும் இதாம்ஸைலேட் மருந்துகளின் செயல்திறன் அறிதல்.

மற்ற பயன்கள்:

- அறுவை சிகிச்சை மற்றும் பிந்தைய காலங்களில் இரத்த ஏற்றத்திற்கான தேவையறிதல்.
- அறுவை சிகிச்சைக்கு பின் ஹெமடோகிரிட் மாறுதல் பற்றி அறிதல்.
-

ஆய்வின் அமைப்பு

பங்குபெறுவோரின் எண்ணிக்கை : 60

அனைவரும் இதய தடுக்கிதழ் (வால்வு) மாற்று அறுவை சிகிச்சை (Cardiac Valve Replacement Surgeries)

குழு 1 : வாய்வழி டிரான்க்ஸாமிக் அசிட் + வாய்வழி இதாம்ஸைலேட்

குழு 2 : இரத்த குழாய் வழி டிரான்க்ஸாமிக் அசிட் + இரத்தகுழாய் வழி இதாம்ஸைலேட்

பயன்கள்:

இதனால் இரத்த கசிவு குறைந்து இரத்த ஏற்றத்திற்கான தேவை குறையும்.

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To

Dr.R.V.Hemalatha
I Year Post Graduate in M.D. Anaesthesiology
Institute of Anaesthesiology & Critical Care
Madras Medical College
Chennai 600 003

Dear Dr.R.V.Hemalatha,

The Institutional Ethics Committee has considered your request and approved your study titled **"PROSPECTIVE RANDOMISED COMPARITIVE STUDY OF EFFICACY OF COMBINATION OF TRANEXAMIC ACID AND ETHAMSYLATE BY ORAL AND INTRAVENOUS ROUTES IN RELATION TO CONTROL OF BLEEDING IN CARDIAC SURGERIES " - NO.14062017**

The following members of Ethics Committee were present in the meeting hold on **06.06.2017** conducted at Madras Medical College, Chennai 3

1. Prof.Dr.C.Rajendran, MD.,	:Chairperson
2. Prof.R.Narayana Babu,MD.,DCH., MMC,Ch-3	: Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4. Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
5.Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC	: Member
6.Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai	: Member
7.Prof. Susila, Director, Inst. of Pharmacology,MMC,Ch-3	: Member
8.Prof.K.Ramadevi,MD., Director, Inst. of Bio-Chemistry,MMC,Ch-3	: Member
9.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
10.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist
11.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

21/6/17

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

MASTER CHART

Group	AGE	Gender	DIAGNOSIS	PROCEDUREDONE	DURATION	HB	PLT	ACT	PT	INR	BT	CT	BLOODLOSS	ACT_A	BLOODTRANSFUSED	VOLUMETRANSFUSED	DRAIN	BLOODTRANSFUSED_A	VOLUME	HB_A	PLT_A	BT_A	CT_A	PT_A	INR_A	ACT_B	Hbdifference
						Pre-op							Intra-op				Post-op										
IV	30	Female	RHD/ MS/ TR/ LA CLOT	MVR+TRA+ LA CLOT REMOVAL	360	15	1.75	152	11.1	0.8	128	340	500	162	NO	0	350	NO	0	14	1	130	250	10.1	0.9	165	1.5
IV	34	Female	RHD/MR/TR	MVR + TRA	360	11	1.45	140	14.8	1.4	138	340	500	182	YES	1	250	NO	0	9.8	1.1	136	355	15.2	1.23	122	1.2
IV	23	Female	RHD/ MS/ TR	MVR + TRA	350	12.2	2.46	146	14.2	1.3	126	180	600	158	NO	0	250	NO	0	10	1.84	124	187	14.4	1.23	166	2.2
IV	21	Female	RHD/ MS/ MR/ AR	DVR	340	10.1	2.4	182	11.6	0.9	142	230	550	101	NO	0	200	YES	2	7.3	1.92	140	237	12.1	1	145	2.8
IV	30	Female	RHD/ MS/ TR	MVR + TRA	330	12.2	4.49	148	11	0.9	142	210	750	120	NO	0	200	NO	0	9.8	3.24	144	210	12	0.8	150	2.4
IV	51	Female	RHD/MS/AS/PHTN	DVR	320	14.8	3.7	136	13.6	0.8	140	220	500	212	YES	1	600	NO	0	13	3.2	142	240	13.8	0.9	145	1.7
IV	37	Male	POST CMC/ MR	MVR	280	13.7	2.01	136	15.1	1.28	150	190	1000	170	NO	0	500	NO	0	12	1.7	149	228	13.9	1	155	1.6
IV	48	Female	RHD/ AS/ AR	AVR	260	12.7	2.6	208	17.6	1.4	136	230	550	247	YES	1	400	NO	0	12	2.1	134	240	16.9	1.5	167	1
IV	60	Male	RHD/ MS/ TR	MVR	260	12.2	2.8	120	13	1.2	138	210	600	160	YES	1	400	NO	0	11	2.3	142	230	13.2	1.24	155	1.1
IV	43	Female	RHD/ MS/ MR	MVR	250	12.8	2.63	170	11.3	0.93	129	210	650	168	YES	1	600	NO	0	12	2.15	125	220	11.4	1.1	134	0.8
IV	55	Male	RHD/ AS	AVR	250	12.3	2.54	142	13	1.3	123	330	1100	144	YES	2	250	NO	0	10	2.1	115	342	13.5	1.5	154	2.1
IV	45	Male	RHD/ POST CMC/ MS	MVR	240	15	2.17	185	11.5	0.9	142	200	500	150	NO	0	250	NO	0	14	1.73	140	210	11.5	0.8	155	1
IV	57	Male	SEVERE AS	AVR	240	10.7	2.2	152	11	1.02	135	220	800	167	YES	2	400	NO	0	10	1.8	140	230	12	1.1	167	0.3
IV	40	Female	RHD/ MS/AF	MVR	230	13.6	2.34	150	20.3	1.5	120	230	800	130	NO	0	300	NO	0	11	1.8	130	260	14.1	1.4	143	2.6
IV	47	Female	RHD/ MS	MVR	230	11.1	3.1	140	10.7	0.89	132	250	350	155	NO	0	300	NO	0	9.2	1.97	135	260	10.7	0.92	156	1.9

IV	**42**	**Male**	**RHD/ MS**	**MVR**	**230**	**10.2**	**3.9**	**128**	**18.2**	**1.3**	**130**	**210**	**300**	**162**	**YES**	**1**	**100**	**NO**	**0**	**9.1**	**3.1**	**120**	**235**	**18.2**	**1.2**	**124**	**1.1**
IV	**52**	**Female**	**RHD/ AS/ AR**	**AVR**	**220**	**14.6**	**3.47**	**135**	**13.2**	**1.1**	**126**	**240**	**450**	**182**	**YES**	**1**	**300**	**NO**	**0**	**13**	**2.8**	**130**	**260**	**13.6**	**1**	**156**	**1.6**
IV	**32**	**Female**	**RHD/ AS/ AR**	**AVR**	**220**	**11.7**	**3.71**	**107**	**12**	**0.99**	**144**	**300**	**500**	**130**	**NO**	**0**	**200**	**NO**	**0**	**9.6**	**4.1**	**140**	**300**	**12.1**	**1.1**	**176**	**2.1**
IV	**52**	**Female**	**RHD/ MS/ MR**	**MVR**	**220**	**10.9**	**2.26**	**253**	**9.8**	**0.82**	**126**	**280**	**1600**	**160**	**YES**	**2**	**450**	**NO**	**0**	**9.2**	**1.75**	**128**	**292**	**9.7**	**0.87**	**145**	**1.7**
IV	**36**	**Female**	**RHD/ MS/ TR/ LA CLOT**	**OMV**	**220**	**9.8**	**2.16**	**248**	**7.6**	**0.65**	**126**	**310**	**600**	**162**	**NO**	**0**	**350**	**NO**	**0**	**8.1**	**1.76**	**128**	**317**	**8.2**	**0.7**	**156**	**1.7**
IV	**40**	**Female**	**POST CMC/ MS**	**MVR**	**210**	**14.1**	**2.92**	**138**	**14.1**	**1.1**	**110**	**320**	**900**	**171**	**YES**	**1**	**250**	**NO**	**0**	**13**	**1.98**	**120**	**220**	**15**	**1.1**	**145**	**1.2**
IV	**37**	**Male**	**RHD/ MS/PCMC STATE**	**MVR**	**210**	**13.7**	**2.05**	**126**	**15.1**	**1.28**	**130**	**220**	**1200**	**100**	**YES**	**2**	**1100**	**YES**	**1**	**13**	**1.09**	**128**	**240**	**14.8**	**1.32**	**134**	**0.9**
IV	**38**	**Male**	**RHD/ MS/ TR**	**MVR**	**210**	**13.6**	**2.8**	**180**	**15**	**1.1**	**128**	**260**	**900**	**168**	**YES**	**1**	**400**	**NO**	**0**	**12**	**2.4**	**130**	**260**	**15.1**	**1.17**	**145**	**1.7**
IV	**55**	**Female**	**RHD/ MS/ SEVERE**	**MVR**	**210**	**11.8**	**1.95**	**130**	**15.7**	**1.2**	**134**	**240**	**700**	**149**	**YES**	**1**	**350**	**NO**	**0**	**11**	**1.45**	**136**	**240**	**15.6**	**1.23**	**156**	**1.3**
IV	**53**	**Female**	**RHD/ MS/ AR**	**MVR**	**210**	**11.8**	**5.42**	**140**	**15.2**	**1.4**	**132**	**230**	**600**	**198**	**YES**	**1**	**450**	**NO**	**0**	**8**	**4.29**	**130**	**247**	**14.8**	**1.5**	**155**	**3.8**
IV	**55**	**Female**	**RHD/ AS/ AR**	**AVR**	**210**	**11**	**3.23**	**152**	**14.1**	**1**	**132**	**260**	**1000**	**162**	**YES**	**1**	**150**	**NO**	**0**	**9.8**	**2.87**	**134**	**260**	**13.9**	**1.2**	**143**	**1.2**
IV	**35**	**Male**	**MVP/ MR/ CCF**	**MVR**	**210**	**10.9**	**1.3**	**165**	**16.3**	**1.17**	**140**	**210**	**400**	**169**	**NO**	**0**	**550**	**YES**	**1**	**8.8**	**0.9**	**144**	**214**	**15.8**	**1.32**	**132**	**2.1**
IV	**60**	**Female**	**RHD/ AS**	**AVR**	**200**	**10.1**	**2.3**	**150**	**14.2**	**1.3**	**132**	**190**	**600**	**174**	**NO**	**0**	**250**	**NO**	**0**	**8.1**	**1.9**	**132**	**211**	**13.2**	**1.4**	**165**	**2**
IV	**35**	**Female**	**RHD/ MS**	**MVR**	**200**	**10**	**2.7**	**208**	**9.8**	**0.82**	**130**	**310**	**400**	**150**	**YES**	**2**	**450**	**NO**	**0**	**8.5**	**2.2**	**128**	**310**	**10.2**	**0.92**	**155**	**1.5**
IV	**34**	**Female**	**RHD/ MS/ MR/ TR/ PHT**	**MVR**	**190**	**11.6**	**2.28**	**160**	**14.8**	**0.9**	**123**	**190**	**450**	**158**	**NO**	**0**	**260**	**NO**	**0**	**9.6**	**1.99**	**125**	**195**	**14.9**	**0.92**	**135**	**2**
Oral	**44**	**Male**	**RHD/MS/AR**	**DVR**	**410**	**10.1**	**2.4**	**182**	**11.6**	**0.9**	**165**	**330**	**1550**	**101**	**YES**	**4**	**200**	**YES**	**2**	**7.3**	**1.92**	**155**	**320**	**10.6**	**0.9**	**155**	**2.8**
Oral	**58**	**Male**	**RHD/ AS/ AR**	**AVR**	**400**	**10.2**	**1.8**	**132**	**18.5**	**1.5**	**148**	**235**	**800**	**180**	**YES**	**4**	**700**	**YES**	**2**	**7.2**	**1.1**	**143**	**245**	**19.5**	**1.6**	**170**	**3**
Oral	**32**	**Female**	**RHD/ AS/ AR/ MR**	**DVR**	**360**	**10.2**	**2.22**	**134**	**12.4**	**1.02**	**167**	**250**	**800**	**168**	**YES**	**4**	**500**	**YES**	**3**	**7.2**	**1.7**	**160**	**234**	**11.1**	**1.1**	**156**	**3**
Oral	**37**	**Male**	**RHD/MS/AR/TR**	**DVR**	**340**	**13.7**	**2.9**	**120**	**15.5**	**1.3**	**134**	**280**	**700**	**154**	**YES**	**2**	**500**	**YES**	**1**	**9.1**	**1.8**	**144**	**299**	**16.5**	**1.4**	**165**	**4.6**

Oral	36	Female	RHD/MS/MR/TR	MVR + TRA	320	11.3	2.2	142	12.6	1.1	125	250	1000	151	YES	3	600	YES	2	9.1	2.4	132	267	12.4	1.1	167	2.2
Oral	53	Male	RHD/ MS	MVR	315	13.8	3.85	140	14.5	1.2	148	238	1000	160	YES	4	300	YES	2	11	3.2	135	245	14.5	1.4	156	2.5
Oral	50	Male	SEVERE MS	MVR	310	12.5	2.8	120	18.1	1.5	110	240	1200	146	YES	3	400	YES	2	8.4	2.6	115	234	18	1.3	154	4.1
Oral	24	Female	RHD/ MS/ MR/ TR	MVR + TRA	300	12.5	2.7	128	14.9	1.2	106	200	900	165	YES	3	200	NO	0	8.7	1.3	110	198	14.9	1	156	3.8
Oral	54	Male	SEVERE AS	AVR	300	12.2	2.8	140	15.1	1.28	154	340	1200	174	YES	3	400	NO	0	8.5	2.5	167	339	14.5	1.2	165	3.7
Oral	60	Female	RHD/ MS/ MR/ AR	DVR	300	10.2	1.9	150	17.8	1.3	125	220	800	178	YES	4	400	NO	0	8.5	1.5	135	218	15.8	1.3	187	1.7
Oral	40	Male	RHD/ AS/ AR	AVR	300	10.1	2.4	182	11.6	0.9	154	300	550	101	YES	2	200	YES	3	7.3	1.92	150	324	11.6	0.8	176	2.8
Oral	37	Male	RHD/ AS/ AR	AVR	250	12.7	2.6	128	17.6	1.4	156	320	550	247	YES	1	400	NO	0	9.5	2.1	167	340	17.4	1.6	144	3.2
Oral	35	Male	POST CMC/ MS	MVR	250	11.2	2.2	120	13.2	1.17	145	300	400	168	NO	0	300	NO	0	11	1.8	156	329	13.3	0.9	160	0.7
Oral	25	Male	BICUSPID AORTIC VALV	AVR	220	14.5	3.1	155	11.2	1	154	300	700	162	NO	0	350	NO	0	9.7	2.3	145	328	11.2	1.3	165	4.8
Oral	40	Male	RHD/ AR	AVR	220	14.2	4.8	120	14.5	1.4	154	240	300	160	NO	0	150	NO	0	12	4.1	150	254	13.2	1.3	156	2
Oral	47	Male	RHD/ MS	MVR	220	14.1	3.9	139	12.8	1.1	145	300	600	187	YES	2	200	NO	0	11	3.2	155	312	11.4	1.3	155	3.6
Oral	47	Male	POST CMC/ MR	MVR	210	15.6	3.68	107	18.1	1.4	155	320	500	149	NO	0	700	NO	#NULL!	10	2.89	144	335	17.1	1	155	5.5
Oral	25	Female	RHD/ MS	MVR	210	14.1	3.5	125	15.5	1.3	152	240	400	130	NO	0	400	NO	0	11	2.5	138	248	15.5	1.4	154	3
Oral	45	Male	RHD/ AS/ AR	AVR	210	13.3	3.5	159	12.5	1.3	145	240	500	133	YES	1	350	NO	0	11	2.6	142	250	12.3	1.3	155	2.1
Oral	55	Female	RHD/ MS/ MR/ AF	MVR	210	12.6	2.6	116	11.8	0.9	175	280	700	153	YES	1	200	NO	0	10	1.9	165	278	12.1	1.02	165	2.4
Oral	23	Male	AR	AVR	210	12.6	1.85	150	13.2	1.12	155	300	1500	147	YES	4	500	NO	0	9.2	1.3	158	312	12.8	1.41	156	3.4
Oral	32	Female	RHD/ MR	MVR	210	11.3	2.3	149	18.3	1.55	119	250	580	158	NO	0	450	NO	0	8.9	1.4	133	244	20.4	1.3	134	2.4
Oral	51	Male	RHD/ AS/ AR	AVR	210	11.2	2.2	120	10.8	1.2	148	230	600	168	NO	0	400	NO	0	9.6	1.6	143	243	11.8	1.5	154	1.6

Oral	**60**	**Male**	**RHD/ MS/ MR**	**MVR**	**210**	**10.5**	**2.5**	**132**	**18.2**	**1.4**	**145**	**245**	**600**	**154**	**YES**	**2**	**700**	**YES**	**1**	**7.1**	**1.7**	**125**	**255**	**18.2**	**1.4**	**145**	**3.4**
Oral	**30**	**Female**	**RHD/ MS/AF**	**MVR**	**200**	**12.1**	**2.9**	**145**	**15.1**	**1.1**	**135**	**280**	**450**	**158**	**NO**	**0**	**400**	**NO**	**0**	**11**	**2.1**	**145**	**297**	**12.8**	**1.4**	**165**	**1**
Oral	**51**	**Male**	**RHD/ SEVERE MS**	**MVR**	**200**	**9.8**	**1.9**	**160**	**16.2**	**0.9**	**105**	**230**	**900**	**148**	**YES**	**2**	**400**	**NO**	**#NULL!**	**8**	**1.3**	**104**	**255**	**16.4**	**0.9**	**165**	**1.8**
Oral	**28**	**Male**	**RHD/ MS/ AR**	**MVR**	**195**	**15.6**	**3.68**	**145**	**15.8**	**1.3**	**135**	**220**	**500**	**157**	**NO**	**0**	**300**	**NO**	**0**	**9.5**	**2.9**	**145**	**240**	**15.7**	**1**	**176**	**6.1**
Oral	**55**	**Male**	**RHD/ MS/ MR**	**MVR**	**195**	**12.1**	**2.9**	**140**	**13.8**	**1.3**	**150**	**240**	**700**	**158**	**YES**	**2**	**300**	**NO**	**0**	**10**	**2.2**	**155**	**234**	**13.9**	**1.3**	**177**	**1.8**
Oral	**38**	**Male**	**RHD/SEVERE MR**	**MVR**	**190**	**10.5**	**2.1**	**178**	**15.2**	**1.2**	**108**	**250**	**500**	**152**	**YES**	**1**	**300**	**YES**	**1**	**10**	**1.7**	**115**	**244**	**15.4**	**1.2**	**157**	**0.2**
Oral	**49**	**Female**	**SEVERE AS/ MODERATE**	**AVR**	**190**	**10.2**	**3.53**	**135**	**12.6**	**1.07**	**134**	**240**	**800**	**175**	**YES**	**2**	**100**	**NO**	**0**	**12**	**2.9**	**143**	**254**	**12.9**	**1.2**	**167**	**-1.4**